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THE EFFECTS OF SULFANILAMIDE, NEOPRONTOSIL AND SULFAPYRIDINE UPON THE ERYTHROCYTE COUNT OF WHITE RATS.

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The purpose of this paper is to present data on the relative effects of administration of equal doses of sulfanilamide (para-aminobenzene sulfonamide), neoprontosil (disodium-4-sulfamido-phenyl-2 azo-7-acetylamino-I-hydroxynaphthalene-3, 6-disulfonate) and sulfapyridine (2 para aminobenzene sulfonamido pyridine) upon the erythrocyte count of white rats. Data will also be presented on the body weight and intake of food and water of the animals which received these drugs.

Wien[4] reported the absence of anemia and porphyrinuria in two groups of 3 rats which received daily doses of sulfapyridine for 15 days; the doses used were 3 and 6 gm. per kg. of body weight respectively in each group. Sulfanilamide, however, when administered in daily doses of 1.5 gm. per kg. of body weight produced both a reduction in the erythrocyte count and an increase in the porphyrinuria. A daily administration of 4 gm. of sulfapyridine per kg. of body weight for 15 days produced a retardation in the growth of young rats which was comparable to that produced by giving daily 1 gm. of sulfanilamide per kg. of body weight. A daily dose of 1 gm. of sulfapyridine per kg. of body weight caused no significant inhibition of growth.

Rimington[3] reported an increased elimination of porphyrin in the urine of rats which had received sulfanilamide and prontosil (soluble). The presence of methemoglobin was demonstrated in the blood of these animals.

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Kreutzmann and Carr[1] reported no change in the erythrocyte and leukocyte counts or in the concentration of hemoglobin of rabbits which received daily intramuscular injections of 0.25 gm. of prontosil for 21 days. An increase in the erythrocyte count, however, was noted following cessation of administration of the drug.

In a previous paper[2] we reported the details of a macrocytic anemia, the toxic symptoms observed and the gross pathologic findings in white rats to which sulfanilamide was administered in various doses for varying periods of time. It was found that adult rats which had received 2 gm. per kg. of body weight lost weight but that animals which received 1 gm. per kg. or smaller doses maintained their body weights very well. Enormously distended stomachs which contained retained food were found in the animals which lost weight. The decrease in the erythrocyte count which was observed was found to bear some relationship to the voluntary daily intake of water by the animals in so far as an increase in the consumption of water occurred and was maintained during a period at which the rate of decrease in the erythrocyte count was lessened.

In the experiments to be reported here, daily doses of each of the three drugs, sulfanilamide, neoprontosil and sulfapyridine, were administered separately to a group of 6 rats for a period of 4 weeks. The rats used were adult males of the Wistar strain; their average weight will be stated in the consideration of the results. The amount of each drug given was 1 gm. per kg. of body weight; each dose was made up to 6 cc. with tap water and was administered by means of a stomach tube. The rats were housed in single cages in groups of 3 and the amounts of food and water consumed were measured daily. The diet consisted of a commercial product which together with fresh water was provided *ad libitum*. Body weights were recorded periodically. The points on the various curves represent the average for the 6 rats of each group. Erythrocyte counts were made at weekly intervals by using samples of blood obtained by puncturing the ear. Platelet counts were made on the group of animals which received sulfapyridine; these counts were made at weekly intervals by the direct method of using a 0.3% solution of sodium citrate as the diluent.

Results. *Sulfanilamide.* The greatest and the most rapid decrease in the erythrocyte count occurred in the group of rats which received sulfanilamide. This decrease was most rapid during the first 2 weeks of the administration of the drug (Table 1), after which the curve depicting the changes in the number of erythrocytes tended to flatten out at the level reached at that time. The average amount of water consumed daily throughout the entire 4 weeks was greater than that during the control period. This increase, however, tended to be greater during the second 2 weeks at which time a further decrease in the erythrocyte count was in abeyance. The average initial body weight of this group was 294 gm. After

a transient decrease observed on the fourth day, which was accompanied by a decrease in the intake of food, the average body weight increased throughout the remainder of the experiment. This increase in body weight was not as great as that of a control group of animals, the latter group gaining an average of 7.2% in 1 month from an initial average weight of 298 gm. The increase in body weight of the group which received sulfanilamide was paralleled by an increase in the daily amounts of food consumed (Chart 1). This group of rats displayed marked cyanosis throughout the entire experiment.

TABLE 1.—EFFECT OF DRUGS ON TOTAL NUMBER OF ERYTHROCYTES OF WHITE RATS.

Drug.	Number of animals.	Dose of drug.	Total number of erythrocytes, millions per c.mm. of blood.				
			Control.	1 week.	2 weeks.	3 weeks.	4 weeks.
Sulfanilamide	6	1 gm. per kg.	9.83±0.12	8.70±0.20	6.95±0.24	7.36±0.13	6.48±0.13
Neoprontosil	6	1 gm. per kg.	10.67±0.14	9.78±0.19	9.62±0.25	8.48±0.16	8.78±0.26
Sulfapyridine	6	1 gm. per kg.	10.07±0.13	10.16±0.18	9.54±0.18	10.05±0.15	9.04±0.20
Controls	6	None	. . . . .	11.16±0.21	10.77±0.18	11.16±0.18	10.87±0.24

Neoprontosil. The average number of erythrocytes per cubic millimeter of blood of the animals which received neoprontosil also decreased during the experiment. This decrease, however, was less marked than that observed in the animals which had received sulfanilamide. Nevertheless, the decrease in the total number of erythrocytes in the blood of animals which received neoprontosil is significant statistically as is indicated by computing the differences and their errors between the control determinations and those of the test animals at the end of each week of administration of the drug (Table 1). The daily intake of food and water by the group which received neoprontosil showed no significant changes throughout the 4 weeks. The average body weight of this group of 6 animals before the administration of the drug was 370 gm. This average weight increased slightly during the first 11 days and then gradually decreased during the remainder of the 4 weeks until it was the same as the weight of the control animals (Chart 2). The control animals gained an average of 6% in weight in the same period of time. The animals that received neoprontosil also displayed cyanosis, but the cyanosis was in no instance as marked as that observed in the group of animals given sulfanilamide.

Sulfapyridine. The group of 6 animals which received sulfapyridine showed the least decrease in the total number of erythrocytes and the slight decrease which was observed was not constantly maintained. At the end of one week there was no change in the

erythrocyte count, but at the end of the second week the mean number of erythrocytes was below that observed during the control period. At the end of the third week the average erythrocyte count had returned to the control level, but at the end of the fourth week it had decreased 10% below the control values. When the data were appraised statistically and the differences together with their errors computed, no significant effect was shown to have been produced until the end of the fourth week. The differences between the mean control value (10.07 ± 0.13) and that attained at the end of the fourth week (9.04 ± 0.20) was 1.03 ± 0.24. This difference, although not large, is statistically significant and the conclusion is thereby indicated that sulfapyridine had induced a slight but real

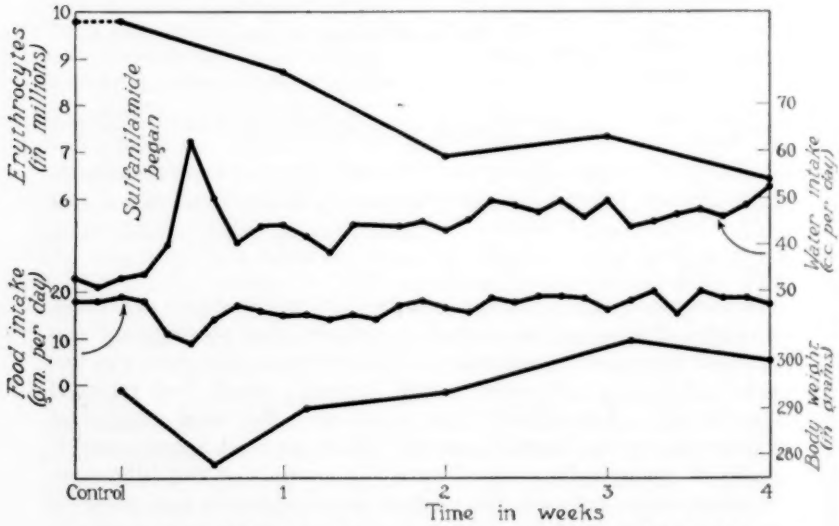

CHART 1.—Trends in the erythrocyte count, body weight and daily intake of food and water of 6 animals which received 1 gm. of sulfanilamide per kg. of body weight daily for a period of 4 weeks.

anemia (Table 1). Erythrocyte counts made at the end of the fifth and sixth weeks upon these same animals, which continued to receive the daily amounts of the drug, remained essentially the same as they did at the fourth week (9.12 ± 0.15 and 9.11 ± 0.37 respectively), but data assembled at the end of the seventh week showed a mean erythrocyte count of 9.67 ± 0.27 million per c.mm. of blood. This figure is not significantly different from the established control values and must indicate that the slight anemia induced by the drug during the fourth, fifth and sixth weeks was but transient. Administration of sulfapyridine was discontinued after the seventh week and sulfanilamide in similar doses was substituted. Within 1 week after the animals had been on sulfanilamide the erythrocyte count decreased to 25% and within 2 weeks to 35% of the orig-

inal value. Platelet counts made at weekly intervals during the first 4 weeks of the administration of sulfapyridine revealed no significant changes. The average platelet counts of 6 animals at weekly intervals were 823,000 (control), 750,000, 830,000, 746,000 and 730,000 per c.mm.

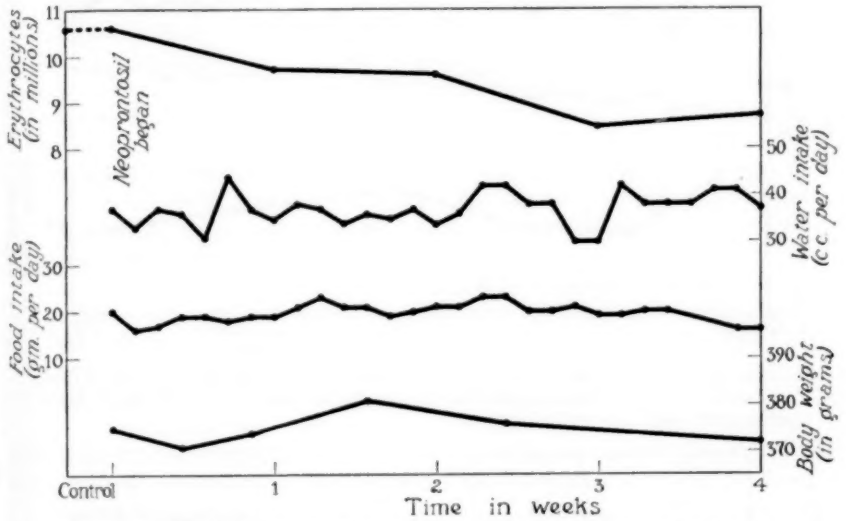

CHART 2.—Trends in the erythrocyte count, body weight and daily intake of food and water of 6 animals which received 1 gm. of neoprontosil per kg. of body weight daily for a period of 4 weeks.

The initial average body weight of the 6 animals which received sulfapyridine was 300 gm. This decreased to 290 gm. on the fourth day of the experiment and thereafter it varied between 290 and and 295 gm. for the remainder of the 7 weeks during which the drug was administered. The average initial body weight of control animals increased 7.2% by the end of the fourth week. There was no significant change in the daily intake of food or water (Chart 3). During the entire 7 weeks cyanosis was not detectable in the group of animals which received sulfapyridine, however, when sulfanilamide was substituted for the sulfapyridine, intense cyanosis soon developed and was maintained.

Comment. The administration of the three drugs in the same amounts daily and by the same route afforded an excellent opportunity to study the effects of these drugs on the erythrocyte count and to observe any possible toxic manifestations which might have occurred. With respect to the erythrocyte count, the results indicate that sulfanilamide depressed the count the most and sulfapyridine the least, while the effects induced by neoprontosil were somewhat in between those produced by the two drugs (Chart 4). Cyanosis was rather intense in the group of animals which received sulfanilamide but was less intense in the animals which received

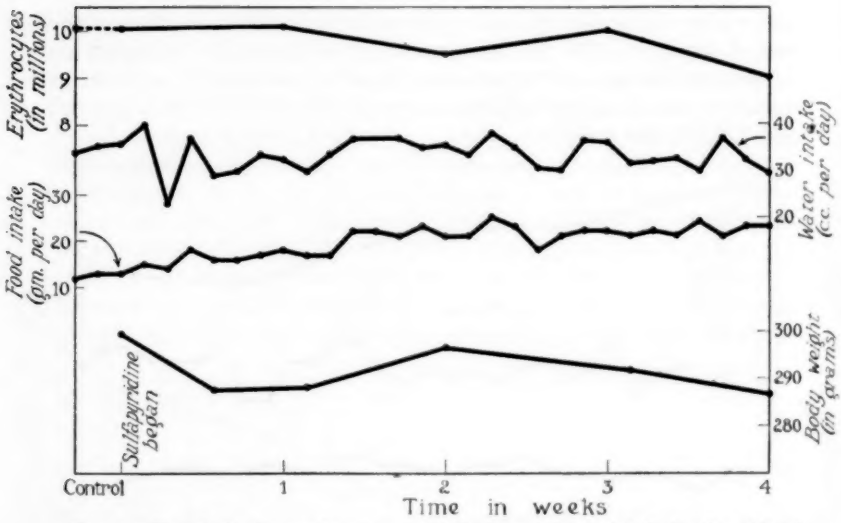

FIG. 3.—Trends in the erythrocyte count, body weight and daily intake of food and water intake of 6 animals which received 1 gm. of sulfapyridine per kg. of body weight daily for a period of 4 weeks.

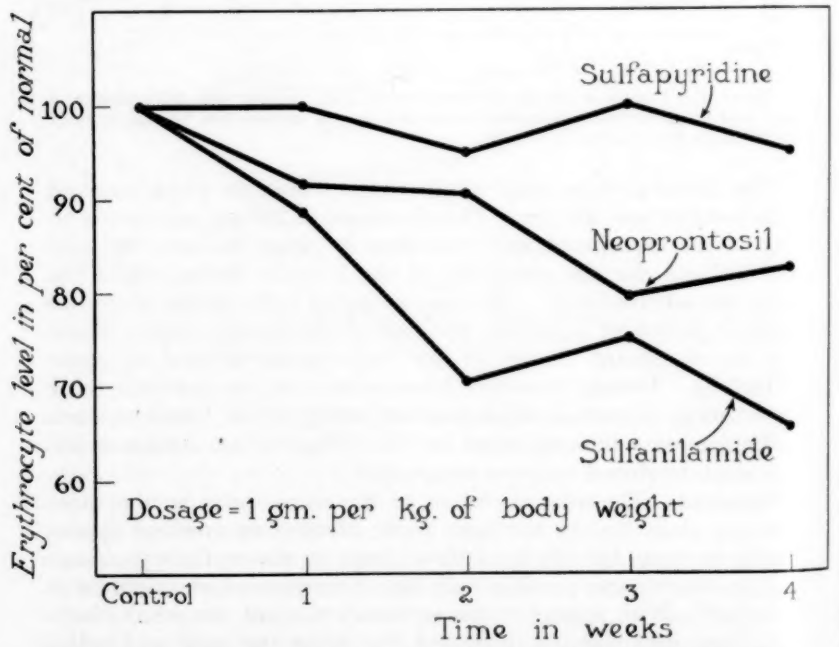

CHART 4.—Comparison of effects of equal doses of sulfapyridine, neoprontosil and sulfanilamide upon the erythrocyte count of rats. The points on the curves represent the erythrocyte counts at the weekly intervals; the erythrocyte counts are expressed as per cent of the normal count.

neoprontosil. Clinical cyanosis was not detectable in the animals which received sulfapyridine. The animals which were used in these experiments were adults, hence satisfactory comparison cannot be made with the results obtained by Wien who used young rats. In our experiments, the animals which received neoprontosil and sulfapyridine failed to gain weight, while controls in the same initial weight ranges did gain. The animals which received sulfanilamide gained slightly in average body weight but not as much as the controls. We have observed loss of body weight in rats which received larger doses of sulfanilamide, including the dose used by Wien (1.5 gm. per kg. of body weight). Convulsions and distended stomachs, the occurrence of which we have already reported in cases in which animals received sulfanilamide in large doses, were not observed in the animals which received sulfapyridine or neoprontosil.

Conclusions. 1. When sulfanilamide, neoprontosil and sulfapyridine were administered in equal doses by the same route, sulfanilamide produced a greater reduction in the total number of erythrocytes than did neoprontosil, which in turn was more potent than sulfapyridine in reducing the red cell count.

2. Cyanosis was more intense in the animals which received sulfanilamide than it was in the group which received neoprontosil; clinical cyanosis was not detected in the animals which received sulfapyridine.

3. All three groups of animals failed to gain in body weight, as compared with controls observed during the 4 weeks of the experiment.

The authors are indebted to Dr. Alfred Uihlein for the platelet counts cited.

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NUTRITIONAL MICROCYTIC HYPOCHROMIC ANEMIA IN DOGS CURED WITH CRYSTALLINE FACTOR I.

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Puppies maintained on a purified casein diet apparently deficient only in Factor I (rat antidermatitis factor, vitamin B_6) developed severe microcytic hypochromic anemia.[3] They also failed to grow

properly and 3 of 4 animals exhibited generalized convulsions. Addition to the diet of a concentrate prepared from rice bran and containing Factor I cured the anemia, but in one animal, in spite of this the convulsions continued. Chick, Macrae, Martin and Martin[1] reported similar findings in young pigs. Feeding of their liver eluate which contained Factor I was followed by resumption of growth, cure of anemia, and disappearance of convulsions.

These findings did not justify the conclusion that the material in rice bran extract and liver eluate which cures rat dermatitis is identical with the substance that cures anemia in puppies and pigs. The purpose of this paper was to ascertain by use of crystalline Factor I whether they are the same. A preliminary report of these observations has been made.[2]

Materials and Methods. Three adult mongrel dogs were fed unrestricted amounts of the synthetic casein diet[3] supplemented daily with 0.05 mg. of thiamine hydrochloride per kilo, 60 micrograms crystalline riboflavin per kilo, 4 cc. per kilo of a liver extract containing Factor II (chick antidermatitis factor) and nicotinic acid but free from Factor I, and halibut liver oil. Dog 2 received in addition 15 mg. of nicotinic acid daily. Supplements were not incorporated in the diet but administered separately. Crystalline Factor I prepared by method of Lepkovsky[4] was used in the studies.

Results. Dog 1 weighed 6.2 kilos when started on the synthetic diet. There was a steady decrease in red blood cell count and hemoglobin after the 22d day of the diet. By the 120th day the red blood cell count had decreased from 8.68 million to 5.16 million per c.mm., hemoglobin from 14.7 to 7.5 gm., hematocrit from 62 cc. to 25 cc. and mean corpuscular volume from 71.4 to 48.4 cubic micra. The dog appeared normal except that she was quieter than usual. Serum-iron on the 113th day was 0.476 mg. per 100 cc.* Oral administration of 60 micrograms of crystalline Factor I per kilo was started on the 127th day when the red blood cell count was 4.52 million, hemoglobin 6.2 gm., and reticulocytes 1.8%; weight was 6.4 kilos. This addition to the supplements was followed by reticulocyte rise to 14% (third day of therapy) and rapid rise in red blood cells and hemoglobin. The weight which had been approximately stationary increased rapidly. Twenty-one days after starting Factor I administration, the red blood cell count was 7.09 million, hemoglobin 14.5 gm., hematocrit 44 cc., mean corpuscular volume 62.1 cubic micra, and weight 8.1 kilos.

The anemia of Dog 2 which developed while on the synthetic diet did not respond to daily oral administration of 0.5 gm. of iron and ammonium citrate and 0.5 mg. copper sulphate. The response of red blood cell count, hemoglobin, and weight to the oral administration of crystalline Factor I was prompt (Table 1). Factor I was

* Blood for serum-iron determinations was collected in iron-free paraffined centrifuge tubes, centrifuged at once and the supernatant serum transferred to glass-stoppered flasks which were mailed to St. Louis where the serum-iron determinations were made. The authors wish to thank Dr. Carl V. Moore for these determinations.

TABLE 1.—RESPONSE OF WEIGHT, RED BLOOD CELL COUNT, HEMOGLOBIN, RETICULOCYTES, HEMATOCRIT, AND WHITE BLOOD CELL COUNT OF DOG 2 TO DIET DEFICIENT IN FACTOR I AND SUBSEQUENT RESPONSE TO CRYSTALLINE FACTOR I.

Day.	Wt. in kilos.	RBC, million per c.mm.	Hgb., gm.	WBC.	Retic., %.	Hem., cc.	MCV.	Remarks.
0	8.1	6.88	12.3	14,700				
6	8.4	6.77	10.8	7,250				
26	8.9	8.11	11.5	9,450				
40	9.1	6.83	11.7	12,200				
54	9.0	7.39	10.2	9,900				
68	9.0	5.47	8.3	7,700				
76	8.8	5.25	8.4	9,100	0.0	31.0	59.0	
78	...	5.25	7.2	10,500	0.4			
83	...	4.61	7.6	11,100	0.0			
84	...	...	...	...	0.4			
85	...	...	...	...	0.0			
86	8.8	5.21	7.0	...	0.0			
87	...	...	...	...	0.0			
88	...	...	...	...	0.0			
89	...	...	...	...	0.0			
90	8.5	4.54	7.0	15,350	0.2	...	...	Serum-iron 0.356 mg. per 100 cc.
91	...	...	...	...	0.8			
92	...	...	...	...	1.8			
93	8.5	4.46	6.6	11,500	1.5			
94	...	...	...	...	1.4			
95	...	...	...	...	0.6			
96	...	...	...	...	1.2			
97	...	4.14	6.5	11,700	1.2	24.0	57.9	
98	8.4	...	...	...	1.2	...	...	0.5 gm. iron and ammonium citrate and 0.5 mg. copper sulphate daily.
99	...	...	...	...	2.4			
100	8.3	4.20	6.7	9,250	1.4			
101	...	...	...	...	1.9			
102	...	...	...	...	1.7			
103	...	...	...	...	2.1			
104	8.3	4.15	5.8	8,000	0.8			
105	...	...	...	...	0.8			
106	...	...	...	...	0.8			
107	8.3	3.64	4.8	11,000	2.3	20.0	54.5	
108	...	4.18	4.5	...	2.5			
109	...	...	...	...	3.5			
110	8.1	3.54	4.8	5,400	2.3	...	...	60 micrograms crystalline Factor I per kilo daily.
111	...	3.72	5.0	4,800	4.6			
112	...	4.16	5.3	6,300	12.0			
113	...	4.53	6.2	5,750	12.8			
114	...	4.86	6.9	7,350	11.5			
115	8.3	4.53	7.2	3,300	9.6			
116	...	...	...	...	10.0			
117	...	...	...	...	5.2			
118	...	4.28	9.2	3,750	4.8			
119	...	5.32	9.2	4,200	2.8			
120	8.5	6.01	10.8	3,800	5.0	35.0	58.2	
125	...	5.01	10.9	3,000	1.3			
129	9.0	5.47	11.2	4,200	1.6			
133	9.1	6.46	14.2	5,700	...	43.0	66.6	
140	...	7.14	14.5	6,950				
141	9.7	...	...	...	...	...	...	Factor I discontinued.
148	9.5	7.04	15.4	11,800	...	45.0	63.9	
176	9.1	6.42	15.4	8,500				
190	9.2	5.06	10.1	7,650				
207	8.6	5.16	9.4	5,750	...	27.0	52.3	
218	8.2	4.46	7.3	7,600	0.6			
221	8.2	3.02	5.9	...	0.0			
222	...	3.12	6.1	...	1.0			
223	...	...	...	...	1.0			
224	...	3.88	7.0	...	3.0			
225	8.0	3.82	8.1	...	4.4	22.0	56.5	
226	...	...	...	...	2.4			
227	...	3.89	6.4	6,900	2.7			
228	7.9	4.02	6.6	...	2.0			
229	...	3.92	5.7	...	1.2			
230	...	...	...	...	1.2			
231	...	3.46	4.8	5,050	1.2			
233	7.8	3.45	4.8	6,250	1.6	17.0	48.9	60 micrograms crystalline Factor I intravenously, daily.
234	...	3.86	6.5	...	8.4			
235	8.0	4.05	6.4	...	6.6	20.5	50.6	
236	...	3.56	5.5	7,900	2.4			
237	8.1	4.44	7.6	8,800	5.6	24.0	54.0	
238	...	...	...	...	4.0			
239	8.4	5.06	9.5	...	4.6			
240	...	4.42	9.7	7,450	5.1	30.5	69.0	
241	...	4.57	9.8	...	6.9			
242	...	5.70	10.9	...	6.2			
243	8.4	5.68	10.9	...	2.6	34.0	60.0	60 micrograms crystalline Factor I, orally.
244	...	...	...	...	5.4			
245	...	...	...	...	3.0			
246	8.9	5.67	10.0	...	1.6			
247	...	5.74	13.3	...	2.0			
254	9.4	5.85	13.3	4,650	...	40.0	68.4	
261	9.4	6.45	12.6	5,600				
289	...	7.55	16.1	7,300				

discontinued after 31 days, although the iron and copper were continued. Within 92 days the hemoglobin was again at a low level. Intravenous injections of Factor I was followed by satisfactory hematologic response and gain in weight (Table 1).

Dog 3 when started on diet weighed 6.9 kilos and the red blood cell count was 7.53 million, hemoglobin 16.2 gm., white blood cell count 10,050, hematocrit 56 cc., and mean corpuscular volume 74.3 cubic micra. Iron and ammonium citrate 0.5 gm. and copper sulphate 0.5 mg. were administered daily after the 114th day. This did not prevent an increasing anemia. By the 136th day the red blood cell count was 5.29 million, hemoglobin 7 gm., white cell count 5500, reticulocytes 0.0%, hematocrit 27 cc., mean corpuscular volume 51 cubic micra, and weight 5.5 kilos. Oral administration of crystalline Factor I was initiated (60 micrograms per kilo daily) and was followed 4 days later by a reticulocyte rise of 6.5%. On the 155th day (19th day of treatment) the red blood cell count was 7.61 million, hemoglobin 14.8 gm., white blood cell count 8800, hematocrit 47 cc., mean corpuscular volume 61.8 cubic micra, and weight 6.9 kilos.

Discussion. These observations show that adult dogs as well as puppies[3] develop microcytic hypochromic anemia when fed a synthetic diet apparently deficient only in Factor I (rat antidermatitis factor, vitamin B_6). The adult dogs were not allowed to become as anemic as the puppies and this might account for the non-occurrence of convulsions in the adult dogs. Iron and copper did not cure the anemia of 2 dogs to which they were administered. In addition, Dog 2 had recurrence of anemia when the crystalline Factor I was removed from the dietary supplements, although the iron and copper supplements were continued. These observations with the finding of high serum-iron values suggest that this microcytic hypochromic anemia is not the result of lack of absorption of iron from the gastrointestinal tract.

The increase in red blood cells and hemoglobin, improvement in appetite, and increase in weight following oral or intravenous administration of crystalline Factor I was as definite as the previously observed responses following rice bran extracts. These results indicate that the material (Factor I) which cures rat dermatitis is identical with that which cures microcytic hypochromic anemia in dogs.

Summary. Adult dogs develop microcytic hypochromic anemia when fed a synthetic casein diet apparently deficient only in Factor I (rat antidermatitis factor, vitamin B_6). This anemia was cured by addition to the diet, or intravenous injection, of crystalline Factor I.

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A PERNICIOUS ANEMIA FAMILY.

Five Authenticated Cases in the Same Generation.

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Richard Cabot,[2] in reviewing the 1200 cases of pernicious anemia reported up to 1908, said "that the disease does not appear to be hereditary." Minot[7] in 1920 finds that the occurrence of the disease in members of the same family is not common and that "a hereditary factor is unimportant." In 1927 he[6] says that "while it is true that pernicious anemia may occur in the same family, this is unusual." But 10 years later Castle and Minot[3] state that "when complete histories are available, at least 18% of the patients will be found to have one or more close relatives who have the disease."

In a study of 32 authentic cases treated here in the last 6 years, 6 instances of the occurrence of the disease in some other member of the family have been verified. This is a familial incidence of 18.7% in an insignificant number of cases. It is our impression, however, from the difficulties experienced in obtaining adequate family histories and in verifying cases, that the true familial incidence is probably higher.

Many of the reports[1,4,5,8–10] of instances of 2 or more cases in one family are based on information obtained from the history or received from other members of the family. Many cases are included which have not been studied or do not fulfill the criteria of authenticated cases of the disease. Wilkinson and Brockbank[10] give a summary of many reports whose analyses show few authenticated and numerous presumptive cases. Patek's[9] and Dorst's[4] reports are outstanding; 4 or 5 members of each family, on whom there are adequate data to justify the diagnosis, having died in the pre-liver era.

For this reason one family with 5 proven cases in one generation is reported together with 5 other families in which the existence of another case of the disease has been verified.

All the cases have been studied with a view to fulfilling the following criteria: suggestive clinical symptoms and findings, a blood picture at some time compatible with the disease, an absolute absence of free hydrochloric acid after the administration of histamine, subjective and objective response to potent liver extract and a period of observation sufficiently long to rule out gastrointestinal malignancy.

Five Authenticated Cases in One Generation. Four brothers have been under treatment for a long time and the 5th case, a sister, has been under treatment since December, 1938. The 6th member of

the family studied, a sister, does not show any suggestive evidence of the disease. There is one other living member of this family whom it has not been possible to persuade to submit to study.

The 4 brothers were seen somewhere, at some time, in a characteristic relapse and responded typically to liver therapy. In all 5 cases the blood smears showed changes compatible with the blood picture of pernicious anemia. In each case a gastric analysis was obtained which showed no free hydrochloric acid after histamine. The blood Wassermann tests were all negative.

Case Reports. Case 1.—H. L. L. (No. 25356, brother), aged 43 (1939). Onset of symptoms at 35. Diagnosis established May 8, 1934. (This was the first member of this family seen.) Two of his brothers were being treated for pernicious anemia and another one had been ill in 1931, but no definite diagnosis had been made. He recognized the similarity of his symptoms to those of his 2 brothers who were under treatment and he had been taking, without consulting a physician, a mixture of liver and iron for 3 years. Red blood cell count 2.3 million per c.mm., hemoglobin 44% (Sahli). Clinically, he answered Addison's description of a case in relapse. There was no objective evidence of postero-lateral sclerosis. Gastric analysis disclosed a total absence of free hydrochloric acid following histamine. He continues well and active with the red count over 5.0 million per c.mm. on a maintenance dose of 1 cc. of liver concentrate every 21 days.

In the spring of 1935 the diagnosis was confirmed at the Mayo Clinic.

Case 2. M. B. L. (No. 30172, brother), aged 47 (1939). Onset of symptoms at 38. Diagnosis established April 21, 1930, at the Northwest Clinic, Minot, North Dakota. Red blood cell count, 1.6 million per c.mm., hemoglobin 52%. Gastric analysis showed no free hydrochloric acid after histamine. Seen here first on November 16, 1935. He wished to change from oral to parenteral liver. Red blood cell count was 4.1 million per c.mm. He has remained well and active with the red blood cell count over 5.0 million per c.mm. on 1 cc. liver concentrate every 21 days.

Objectively, at the time I saw him, his general examination was negative including the examination of the central nervous system. In June, 1925, he had been treated for lues at the Mayo Clinic and in January of 1926 the gall bladder was removed there. Both in 1925 and 1926 gastric analyses showed an absence of free hydrochloric acid. Symptoms of the pernicious anemia did not appear until 1930.

Case 3.—T. J. L. (No. 23604, brother), aged 57 (1939). Onset of symptoms at 49. Diagnosis established December 28, 1935. Red blood cell count 3.8 million per c.mm., hemoglobin 58%. The blood smear showed many well-filled macrocytes. Two subsequent blood counts showed color indices well above one. His color was suggestive; tongue smooth; knee jerks were increased and vibratory sense was diminished to absent in the ankles. His symptoms disappeared promptly with the use of parenteral liver extract. He is well and active with a red blood cell count above 5.0 million per c.mm. on 1 cc. of liver concentrate every 10 days.

He had been seen here in 1931 because of numbness and tingling of the hands and feet. He was seen again in October, 1933, with gastro-intestinal complaints which led to a gastric analysis which showed no free hydrochloric acid after histamine; red blood cell count was 5.0 million per c.mm., hemoglobin 80%. In May, 1934, H. L. L. (Case 1) at my request, urged T. J. L. (Case 3) to report for examination, which he finally did in December, 1935. He was forced to report by increase in severity of symptoms characteristic of pernicious anemia, referred to the gastro-intestinal, cardiovascular and nervous systems.

CASE 4.—J. M. L. (No. 30973, brother), aged 63 (1939). Onset of symptoms at 56. Diagnosis established in 1932, on clinical grounds and on the results of liver therapy, by his local physician. Progressive weakness had made him unable to walk a block. Three and one-half pounds of fresh liver a week brought his hemoglobin from 56 to 87%; no red blood cell count. Gastric analysis at that time showed no free hydrochloric acid; histamine was not given. In only fair health on 4 ounces of powdered liver daily.

He was seen for confirmatory study June 2, 1936. Red blood cell count 3.4 million per c.mm., hemoglobin 80%. Blood smear showed many macrocytes and microcytes. Gastric analysis showed no free hydrochloric acid after histamine. Tongue smooth, color lemonish, knee jerks exaggerated, vibratory sense diminished to absent in both ankles. A change to parenteral liver brought the red count above 5.0 million per c.mm. promptly. He is still well and active with a red blood cell count above 5.0 million per c.mm. on 1 cc. of liver concentrate every 7 days.

CASE 5.—Mrs. L. N. B,* sister, aged 66 (1939). Onset of symptoms at 64. Diagnosis established August, 1938. The following data obtained by correspondence: On July 22, 1938, the red blood cell count was 3.4 million per c.mm., hemoglobin 81%, and a gastric analysis showed an absence of free hydrochloric acid; no histamine. On August, 18, 1938, the gastric analysis was repeated and showed no free hydrochloric acid after histamine. The red blood count, repeated on this date had dropped to 3.0 million per c.mm., hemoglobin 80%. Blood smears forwarded from the local laboratory showed many well-filled macrocytes and a few microcytes. She had been receiving medical attention since 1937 for paresthesias of the hands and feet. By December, 1938, her general condition was much worse; she was placed on parenteral liver therapy and is now (June, 1939) much improved.

NOTE: Mrs. J. C. C. (No. 38035, sister), aged 55 (1939). Reported for study on March 31, 1938. Nothing suggestive of pernicious anemia subjectively or objectively. Red blood cell count was 4.7 million per c.mm., hemoglobin 86%. The blood smear was normal in appearance. Gastric analysis showed an abundance of free hydrochloric acid without histamine.

NOTE.—E. R. L., brother, living in Nevada, aged 50. Neither the author nor the other members of the family, who have been most coöperative during the 5 years of this study, have been successful in persuading him to submit to examination.

TWO CASES IN EACH OF FIVE FAMILIES.

CASE 6.—A. O. T. (No. 18394, seen here), aged 32 (1939). Onset of symptoms at 24. Diagnosis established January, 1931. Red blood cell count 1.7 million per c.mm., hemoglobin, 50%. Repeated gastric analyses have failed to show free hydrochloric acid after histamine. Relapse in June, 1932, red blood cell count 1.5 million per c.mm., hemoglobin, 37%. Relapse in 1935, red blood cell count 1.4 million per c.mm., hemoglobin, 32%. In 1935 he showed marked objective evidence of combined sclerosis. He responded well to liver therapy at the time of each relapse. Since 1935 arrangements have been made so that he obtains parenteral liver regularly. He works, slightly handicapped by his cord changes.

CASE 7.—Mrs. C. T. T. (No. 5669, seen here, mother of A. O. T.), aged 67 (1939). Onset of symptoms at 63. Diagnosis established September 9, 1936. Red blood cell count 1.9 million per c.mm., hemoglobin, 30%. Gastric analysis showed no free hydrochloric after histamine. Vibratory sense in the ankles was absent. Roentgen-rays of the stomach and colon showed no evidence of malignancy. She made a typical therapeutic response to liver extract. In only fair health since, she is irregular about her liver and the red blood cell count is rarely well up.

* Information through the courtesy of Dr. A. J. Lewis, Henning, Minn., and Mildred Nichols, R.N., Wadena, Minn.

Three years before the establishment of the diagnosis she was seen with the complaint of fatigability; red blood cell count then was 3.3 million per c.mm.; hemoglobin, 58%. Diagnosis confirmed in 1937 by Dr. L. J. Meienberg, Portland, Oregon.

Case 8.—Mrs. D. A. S. (No. 13568, seen here), aged 48 (1939). Onset of symptoms at 39. Diagnosis established in January, 1930. Gastric analysis showed no free hydrochloric acid after histamine. Subjective symptoms of numbness of the hands and feet. Blood smears showed a picture compatible with pernicious anemia. Carried on oral liver until relapse in 1936; moderate spinal cord changes. Lowest red blood cell count 3.0 million per c.mm.; hemoglobin, 60%. Therapy complicated by the presence of myxedema. Typical therapeutic response to larger than usual doses of liver. Maintained in good health at about 5.0 million red blood cells per c.mm. on 5 cc. of liver extract each week up to the present time.

Case 9.—L. H. B.* (No. 16509, brother of Mrs. D. A. S), aged 65 (1939). Minimum red blood cell count report showed 2.6 million per c.mm. After the first use of liver extract a count was obtained on October 27, 1938, which showed 3.4 million per c.mm.; hemoglobin, 80%. Blood smear was perfectly compatible with pernicious anemia. The gastric analysis showed no free hydrochloric acid after histamine.

Case 10.—R. M. (No. 38075, seen here), aged 71 (1939). Onset of symptoms at 69. Diagnosis established in March, 1938. Red blood cell count 4.6 million per c.mm.; hemoglobin, 88%. The blood smear showed many macrocytes and microcytes and in other features was entirely compatible with pernicious anemia. In spite of the high red blood cell count, there was evidence of advanced spinal cord involvement; total absence of vibratory sense in both ankles and a strikingly abnormal gait. The gastric analysis showed no free hydrochloric acid after histamine. He refused treatment for a month during which time he became unable to walk. Responded slowly but steadily to large doses of parenteral liver daily for many weeks. At present, he is in good health except for some residual disturbances and gets about actively without the use of a cane. His maintenance dose is 3 cc. of liver concentrate derived from 100 gm. of liver, every 5 days.

Case 11.—J. J. M.,† (brother of R. M.), seen in February, 1925, in the Jefferson Medical School Hospital on account of a sore mouth and paresthesias of the extremities. Red blood cell count 2.2 million per c.mm.; hemoglobin, 52%. Roentgen-rays of the stomach led to an exploratory operation which disclosed no malignancy. Red blood cell count 2.2 million per c.mm.; hemoglobin, 57% in July, 1925. Total absence of free hydrochloric acid in the gastric analysis (histamine was not used). He was not seen after July, 1925. He became helpless and died of "anemia and paralysis" about a year later. No liver therapy.

Case 12.—Mrs. L. M. C. (No. 36653, seen here), died January, 1938, at the age of 71, of cardiovascular disease. Onset of symptoms at 66. Diagnosis established in 1932 at the Mayo Clinic. Records available show fairly satisfactory maintenance through 1935, following which she had no medical attention until she was admitted to the hospital on September 28, 1937, with a red blood cell count of 1.4 million per c.mm.; hemoglobin, 46%. Prompt response to heavy dosage of parenteral liver brought the blood to 4.0 million per c.mm.; hemoglobin to 84%. Maximum reticulocyte response 40%. Vibratory sensation was absent in the ankles.

Case 13.—H. G. B.‡ (brother of Mrs. L. M. C.), aged 62 (1939). Onset of symptoms at 57. Diagnosis established at the County Hospital, Los Angeles, at time of relapse. Blood data not available. He made the

* Verification through the courtesy of Dr. H. W. Pfeiffer, La Mesa, California.

† Verification through the courtesy of Dr. E. J. G. Beardsley, Philadelphia.

‡ Verification through the courtesy of Dr. J. M. Askey, Los Angeles.

typical response to oral liver, on large doses of which he has done well for 5 years. Examination on April 10, 1939, showed an absence of vibratory sense in both ankles with increased patellar jerks.

CASE 14.—Mrs. C. A. B. (No. 04431, seen here), aged 66 (1939). Onset of symptoms in 1928. Diagnosis established August, 1928. Red blood cell count, 2.1 million per c.mm.; hemoglobin, 70%. Liver and powdered liver extract orally gave unsatisfactory maintenance and disabling spinal cord changes by 1932. Histamine achlorhydria. Improved since, with red blood cell count maintained above 4.5 million per c.mm. on 3 cc. liver concentrate every 7 days.

CASE 15.—J. S.* (brother of Mrs. C. A. B.), aged 63 (1939). Onset of symptoms in 1926. Diagnosis established in June, 1927, at the University Hospital, Ann Arbor, Mich. Red blood cell count, 2.4 million per c.mm.; hemoglobin, 49%. Typical response to whole liver. Histamine achlorhydria. Well and active since on diet of whole liver. Red blood cell count in April, 1938, 4.9 million per c.mm.; hemoglobin, 96%, at the Simpson Memorial Institute.

Comment.—Meulengracht[8] pointed out the difficulties inherent in any study of the familial incidence of this disease; difficulties due to errors in diagnoses, to the scattering of families, and to the development of the disease late in life. Five years were required to obtain the data on the few cases reported here and the data had to be obtained from widely separated geographical points (Philadelphia to Los Angeles). The mother of the son who developed the disease at age 24 did not herself develop the disease until age 63; her death at age 60 of pneumonia would have excluded these cases from the study. The physician in practice can best follow several generations of a family and he is, therefore, in an enviable position for the accumulation of data.

The practical value of an appreciation of the true familial incidence of the disease is as great as in diabetes mellitus. It justifies anticipatory studies which should lead to the earlier recognition of the disease, especially in those cases in which "diagnostic" blood changes lag well behind spinal cord changes.

Summary. 1. A pernicious anemia family is reported with 5 authenticated cases in one generation.

2. Two cases are reported in each of 5 other families.

3. In this small series of cases the percentage of familial incidence is 18.7% which approaches the 18% found by Castle and Minot.

4. It is suggested that the true incidence is higher and that an appreciation of the familial incidence has definite practical value.

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* Verification through the courtesy of Dr. R. Isaacs, Ann Arbor, Mich.

SOME OBSERVATIONS UPON A CASE OF HEREDITARY HEMOLYTIC JAUNDICE.

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In 1935 the senior author[3] reported studies on a case of pernicious anemia in an individual having hereditary hemolytic jaundice. It was pointed out that in spite of the presence of the pernicious anemia the erythrocytes maintained the relatively small diameter and spherical shape of hemolytic jaundice. Following liver therapy, marked improvement occurred and all evidence of pernicious anemia disappeared. However, the characteristic features of hemolytic jaundice have persisted and are uninfluenced by the therapy. On two occasions since his discharge from the hospital the patient has neglected to take his liver extract and a recurrence of the pernicious anemia has taken place, but in each case improvement followed a return to adequate treatment. Because of the age of this patient (67) it has not been considered advisable to recommend splenectomy.

At the time this study was reported, blood studies were carried out on 3 of his children and hemolytic jaundice was found to be present in 1 son, then 32 years of age. This individual showed no evidence of pernicious anemia and gastric analysis revealed free hydrochloric acid. The spleen was large, extending 10.5 cm. below the border of the ribs, and he was advised to have it removed. He would not consent, however, and his health was not markedly disturbed by the condition. In the interval he has remained quite well, but recently a severe exacerbation brought him to the hospital and consent was obtained to proceed with the splenectomy. As opportunity was thus given to make detailed studies on a case of hereditary hemolytic jaundice which had been under observation for some time, special examinations were carried out. Because of the more precise methods in estimating hemolysis of the erythrocytes and bilirubinemia made possible by the use of the Evelyn photoelectric colorimeter, certain new facts were brought out by these studies and it is the purpose of this communication to present them to the literature.

Clinical History. The patient was admitted to this hospital on Jan. 3, 1939, with complaints of: 1, increasing jaundice of 4 days' duration; 2, pain in the left side of the abdomen and left shoulder continuously for 4 days; and 3, vomiting on 1 occasion 4 days prior to admission. The patient complained that the pain in his left side and left shoulder was worse

upon lying down flat. He had noticed that his jaundice appeared to be deeper at intervals ranging from 10 days to a month over a period of many years, also that any slight infection, especially of the upper respiratory tract, made it more pronounced. He had never had an attack associated with pain in the left shoulder and left side of the abdomen previous to the one from which he was suffering.

Physical examination revealed temp. 100.6° F., pulse 112, respirations 22 per minute. Blood pressure 132/75. There was a moderate degree of jaundice. The abdomen was slightly distended. The liver was palpable 2 finger-breadths below the costal margin. The spleen was 3 finger-breadths below the costal margin and was exquisitely tender. Physical examination was otherwise negative. Roentgen rays of the chest and abdomen revealed gross enlargement of the spleen, slight elevation of the left diaphragm with left diaphragmatic pleuritis. A diagnosis of familial hemolytic jaundice, left diaphragmatic pleuritis and upper respiratory infection was made.

Clinical Notes and Progress. On admission to the hospital on January 3 the patient was in the midst of a severe attack of jaundice. This gradually subsided, with clinical improvement of the patient, until Feb. 3, 1939, at which time he suffered a recurrence of the upper respiratory infection and an accompanying increase in jaundice. There was gradual clinical improvement with subsidence of the upper respiratory infection and decrease in symptoms until the time of operation.

The patient's spleen was removed on February 10. Following operation there was a marked increase in upper respiratory symptoms but a definitely progressive improvement in jaundice and relief of pains. He was discharged on March 6, at which time jaundice had completely disappeared and there was no evidence of infection. Follow-up examination on April 21, 1939, showed the patient to be free of jaundice and to have gained 20 pounds in weight since discharge from the hospital.

Pathologic Examination. The spleen was large (1750 gm.) and markedly hemorrhagic in appearance. There was a large subcapsular hematoma at the upper pole. The capsule was densely thickened by fibrous tissue. Microscopic examination showed the pulp to be stuffed with blood while the venous sinuses were collapsed. The spleen was therefore typical of that found in hereditary hemolytic jaundice.

Hematologic Examination (first, Feb., 1937). *Bilirubinemia.* At that time he appeared to be suffering from one of the exacerbations of jaundice to which he was subject. The blood bilirubin at that time showed a total bilirubin of 28 units van den Bergh. The prompt direct van den Bergh reaction was negative; the delayed direct reaction was strongly positive. Photoelectric determinations were unfortunately not available at that time.

On admission to the hospital, January 3, 1939, the patient was again in the midst of a severe attack of jaundice. At that time the total bilirubinemia, as determined by the method of Malloy and Evelyn,[2] was 11 mg. per 100 cc., of which 2.31 mg. gave the direct reaction. The direct reaction was 51% complete at the end of ½ minute and 100% complete at the end of 10 minutes.

Following hospitalization the patient showed considerable improvement, with decreasing bilirubinemia (see Chart 1), so that 18 days after entering hospital the total bilirubinemia had reached 3.9 mg. per 100 cc., of which 0.73 mg. was present in the direct reaction. This was 51% complete at the end of ½ minute and 85% complete at the end of 10 minutes.

On February 3, the patient suffered an exacerbation of his jaundice, accompanied by an increase in the size of the spleen and corresponding increase in the pains in the left side of his abdomen and left shoulder. On the thirtieth day after admission the total bilirubinemia was 6.5 mg., of

which 0.81 mg. gave the direct reaction. This was 51% complete at the end of ½ minute and 84% complete at the end of 10 minutes.

Following this episode there was a period of clinical improvement and on the day preceding operation the patient showed a total blood bilirubin of 4.8 mg. per 100 cc., of which 0.68 mg. was direct bilirubin. The direct reaction was 17% complete at the end of ½ minute and 93% complete at the end of 10 minutes.

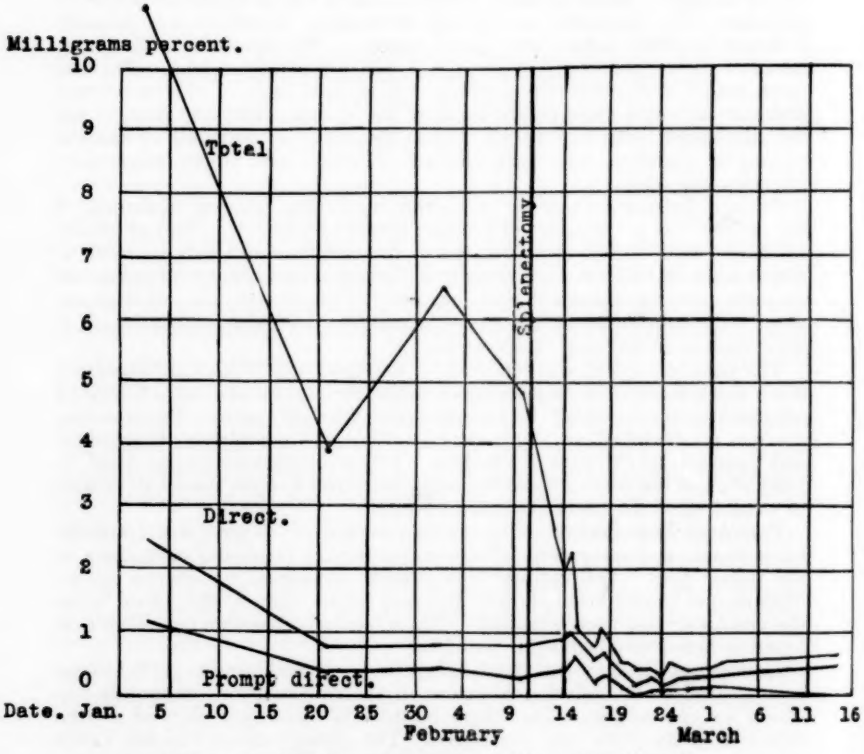

CHART 1.—Hereditary hemolytic jaundice. Bilirubinemia.

Splenectomy was performed on February 11. Two days later the bilirubinemia had dropped to 2.6 mg. per 100 cc., of which 0.91 mg. was direct bilirubin. The direct reaction was 31% complete at the end of ½ minute and 88% complete within 10 minutes.

Following this the bilirubin dropped rapidly so that 6 days after operation the total bilirubin was below 1 mg.; 9 days after the total bilirubinemia was close to normal limits. Jaundice disappeared clinically at the same time and has not recurred. Thirty-four days after operation the total bilirubin of the blood was 0.68 mg., of which 0.33 mg. was contained in the direct reaction. The immediate direct reaction was negative at ½ minute and 33% complete at the end of 10 minutes.

As has been recognized for some time, our findings show that this hyperbilirubinemia of hemolytic jaundice is due principally to the large amount of bilirubin in the circulating blood giving the indirect

reaction. The finer details of the photoelectric method reveal, however, that there is an appreciable increase in the direct-reacting bilirubin which rises somewhat in exacerbations but tends to maintain a fairly constant level of approximately 0.7 to 0.9 mg. per 100 cc. Following splenectomy there occurs a precipitous fall in indirect bilirubin with an accompanying slight rise in the direct bilirubin. Finally, after the total bilirubin has reached a figure of about 1 mg. the two types gradually fall together to essentially normal levels.

Red Blood Cell Fragility. Studies in the fragility of the erythrocytes to hypotonic solutions of salt were carried out, using the recently published method of Waugh and Asherman.[4] By this method the resistance of the cells may be expressed either as an

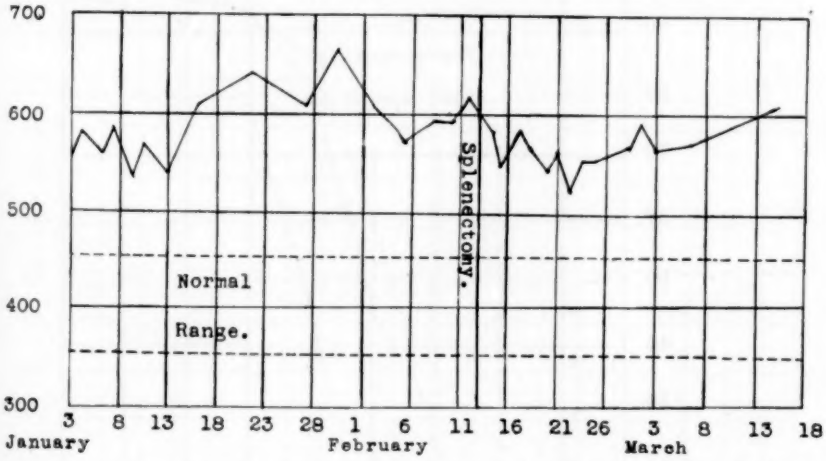

CHART 2.—Hereditary hemolytic jaundice. Index of hemolysis (before and after splenectomy).

index, which has a normal range from 350 to 450 and which falls as low as 250 in cases with lessened, and as high as 750 in increased fragility, or as a so-called hemolygram in which a chart expressing the character of the curve of resistance throughout the different concentrations is employed.

The index of hemolysis in this case was found to be consistently well above normal limits (Chart 2) and at a relatively constant level, which tended to fall slightly following operation but subsequently rose to its previous figure. It is well known that splenectomy produces an increase in the resistance even in normal individuals (accident cases), so this fall is rather to be expected. It is noteworthy, however, that the increased fragility persists even though the excessive destruction of the erythrocytes ceases when the spleen is removed.

By the use of the hemolygram (Chart 3), an interesting change in the character of the fragility curves before, as compared with those

after operation, was disclosed. It will be noted that during the preoperative period the curve becomes distinctly irregular in the higher concentrations, due to the presence of a number of cells which hemolyzed in the higher, even isotonic solutions. This feature, which was persistent before, however, completely disappeared after operation and the curve then became quite regular and similar to the normal, though displaying a distinct shift of position toward an increased fragility.

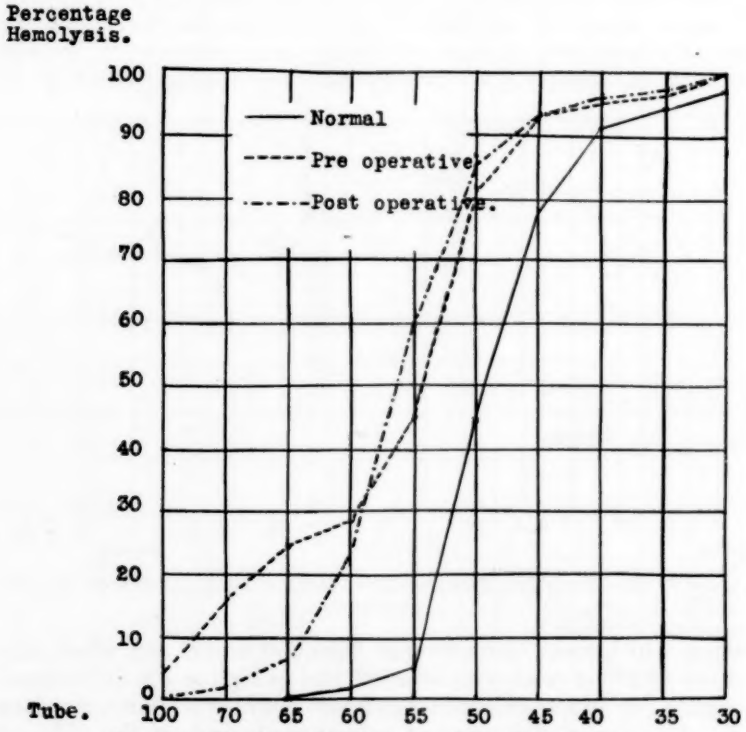

CHART 3.—Hereditary hemolytic jaundice. Hemolygram.

Removal of the spleen evidently caused the disappearance from the blood of a certain percentage of extremely fragile cells, while the great majority of the erythrocytes remained as before. As the reticulocytes tend to decrease after operation, one might surmise that they are the forms concerned. Such an opinion does not agree with the generally accepted view that reticulocytes are not unusually fragile. While we are unable to explain this peculiar change, we cannot help but feel that it may be of considerable significance and, if it is found to be present in other cases of this disease, may even be considered as a possible explanation of the beneficial effect of splenectomy.

Red Blood Cell Diameter. Studies of the diameter of the erythrocytes were made by a specially constructed apparatus whereby the cells are projected at a magnification of 5000 onto a ground glass

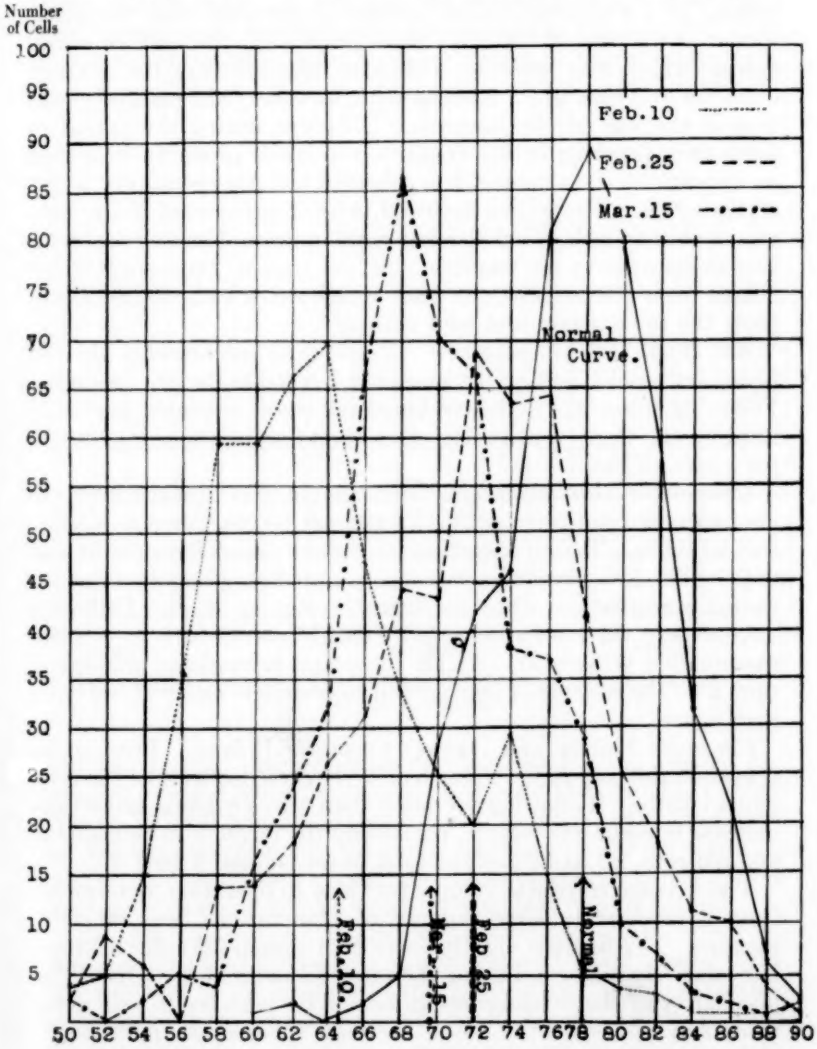

CHART 4.—Hereditary hemolytic jaundice. Price-Jones curves. Mean corpuscle diameters of individual cells in 0.1 microns. Arrows indicate computed average corpuscle diameters.

plate. The maximum and minimum diameter of 500 cells are recorded and from this a so-called Price-Jones curve is constructed and the average diameter computed. In Chart 4, several of these

curves are shown together with a normal for comparison. It will be noted that on February 10, just prior to splenectomy, the average diameter of the erythrocytes was 6.44 microns, in contrast to the normal of 7.8 microns. The lowness of the peak and the great spread of the base of the curve show graphically the marked anisocytosis which was present. Following splenectomy, the average diameter first rose to 7.2 microns with, however, still marked variation in the size of the elements. This was during the period of temporary lowering of the fragility and quite probably indicated an appearance of flattening, less spherical but not necessarily larger erythrocytes. There then occurred, with improvement in the anemia, a shift to cells of smaller but more uniform diameter and with this an increase in the fragility. At the time of the patient's discharge from the hospital, the peak of this curve had reached essentially the same height met with normally.

Red Blood Cell Enumerations. Previous to splenectomy the red blood cell count had never exceeded 3,800,000 on any occasion. Following splenectomy the red blood cell count increased gradually until on the thirty-second day after operation it reached 4,700,000 per c.mm. of blood.

Hemoglobin Determinations. Hemoglobin was measured by the photoelectric colorimeter with 15.6 gm. per 100 cc. taken as equivalent to 100%. Before operation the figures varied between 54 and 68%. The lower readings were encountered as would be expected during exacerbations when the bilirubinemia was high. Following splenectomy there occurred a quite steady rise to 96% at our last examination (Chart 5). At all times the hemoglobin concentration, *i. e.*, the relation of hemoglobin to corpuscle material, was at a high figure.

Corpuscle Volume and Average Corpuscle Volume. Previous to operation the corpuscle volume had never exceeded 34% of the total blood volume. Following operation there was a gradual and steady increase in corpuscle volume, paralleling the increase in hemoglobin and red cells, up to 45% of the total blood volume (Chart 5).

The average corpuscle volume previous to operation, determined from a moderately large number of observations, was 90 cubic microns. This figure is slightly lower than normal (95 cubic microns) but relatively high considering the small diameter of the cells. This peculiarity of the erythrocytes in hemolytic jaundice is well recognized and has led to the use of the term spherocytes, indicating a cell of spherical, rather than biconcave shape. This alteration of shape is now generally accepted as the explanation for the increased fragility. After splenectomy the average corpuscle volume fell somewhat but the general spherical character of the cells was preserved.

Reticulocyte Counts. Reticulocyte counts done before operation showed levels often as high as 15%, and never below 1% of the

total red blood cells. Following operation, the reticulocytes in the circulation rapidly decreased so that within 12 days they had reached normal levels or less than 1%. Thus, as has often been shown before, with the cessation of abnormal blood destruction after splenectomy, hurried regeneration and the discharge of many immature erythrocytes into the blood stream no longer occur.

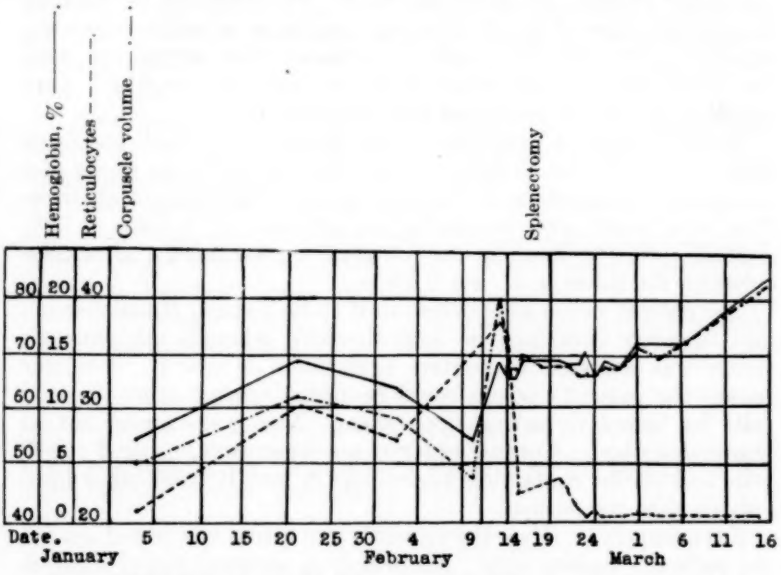

CHART 5.—Hereditary hemolytic jaundice. Hemoglobin, corpuscle volume and reticulocyte count.

Platelet Counts. Enumeration of the thrombocytes carried out during the period preceding operation showed the platelets to vary between 135,000 and 330,000 per c.mm. of blood. On the fourth day following splenectomy the count reached 610,000 per c.mm., a definite elevation above normal. This elevation persisted for 1 month, at the end of which time it gradually fell to normal.

Leukocyte Counts and Differential Leukocyte Counts. Prior to operation the blood showed a constant leukocytosis of around 9000. This was due to an increase in the myeloid elements. Following splenectomy there was a sharp rise to 40,000 due to the pouring into the blood of neutrophils, eosinophils and monocytes. This gradually fell off until by March 1 it again reached 9000, which level has been maintained. Such a moderate persistent increase in the white blood cells is usual following removal of the spleen.

Study of the Blood Serum to Determine the Presence or Absence of Hemolysins. Previous to operation an attempt was made to determine the presence of hemolysins in the blood serum of the patient, as

suggested by Dameshek and Schwartz[1] in their article on acquired hemolytic jaundice.

The technique of the investigation was as follows: The patient's blood was allowed to clot for at least 4 hours and the serum withdrawn. Increasing dilutions from 1 to 2 to 1 to 2048 were made up in 11 tubes. A suspension of red blood cells from the patient and other sources, as mentioned below, was prepared by washing the red cells three times in saline and making up a saline suspension containing 1% red blood cells. Titrations were carried out with the above dilutions of serum in 0.5 cc. amounts, to which were added 0.5 cc. of the red blood cells suspension.

Repeat titrations were carried out using serum which had been heated to 56° C. for 30 minutes. To this was added an excess of a solution of complement of known potency. Readings of all titrations were made after incubating the titration for 2 hours at 37°; secondly, after 18 hours in the refrigerator and, thirdly, after reincubating the tubes at 37° for 2 hours.

The patient's cells were determined to be Type O (Landsteiner), and therefore contained no agglutinogens; whereas the patient's serum was assumed to contain agglutinins A and B. For this reason the patient's serum could be tested against other Type O cells for hemolytic action upon them. This was carried out as above described. Control experiments were done, using Type O cells and serum containing agglutinins A and B from other individuals than the patient.

EXPERIMENT 1. Here the patient's own serum was tested against the patient's washed cells. No hemolysis occurred in any dilution in any of the three readings.

EXPERIMENT 2. The patient's serum, heated to 56° for 30 minutes was tested against the patient's washed cells, excess complement in the form of diluted guinea pig serum being added. No hemolysis occurred in any tube in any of the three readings.

EXPERIMENT 3. The patient's serum was tested against Type O cells which previously had shown no signs of agglutination with the patient's serum, to obviate any error that might arise from using cells which might contain agglutinogens not tested for with the routine serum. There was no evidence of any hemolysis in any of the three readings in any of the tubes.

EXPERIMENT 4. The patient's serum, heated to 56° C. for 30 minutes was tested against Type O cells which fulfilled the characteristics sought in Experiment 3. Excess complement was added to each tube. No hemolysis occurred in any of the tubes on any of the three readings.

EXPERIMENT 5. Type O cells were tested against the serum from the same individual, not the patient. No hemolysis occurred in any tube.

Our experiments, therefore, failed to demonstrate the presence

of any hemolysin which could be brought into causal relation with the excessive destruction of the erythrocytes which was present.

Summary. Special detailed hematologic studies carried out in a case of hereditary hemolytic jaundice before and after splenectomy, besides substantiating many well-known facts, reveal:

1. The direct-reacting bilirubin of the blood plasma tends, in contrast to the indirect-reacting portion, to maintain a relatively constant level, even during exacerbations; rises slightly immediately following splenectomy and then falls when the total bilirubin reaches 1 mg. per 100 cc. to normal levels.

2. The hemolytic index of the erythrocytes is not appreciably altered by splenectomy except for a temporary slight fall immediately following operation.

3. There are present in the circulating blood before operation a small percentage of extremely fragile cells, and these disappear after splenectomy, though the vast majority of the cells are apparently not altered in their behavior to hypotonic salt solution.

4. No hemolysins for the patient's own cells or cells of a like group are present in the plasma.

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THE POTENCY OF BLOOD-COAGULATING SUBSTANCES.

A Biologic Assay.*

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There are, in general, three types of hemostatic agents: those that act by decreasing the blood flow, those that promote repair of diseased blood-vessels, and those that increase the coagulability of the blood. In effective dosage, many of the substances of the third group cause toxic reactions, induce necrosis, or produce widespread intravascular coagulation.

When contemplating the use of a blood-coagulating substance, it is important to know the answers to three questions: Is the

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substance safe to administer? How effective is it *in vivo?* What is its potency *in vitro?* This paper deals with the biologic assay of the potency of a group of commercially available substances purporting to increase the coagulability of the blood.

It can be shown experimentally *in vitro* that the coagulation of the blood does not take place according to the law of mass action. The coagulation of the blood cannot be accelerated by the indiscriminate addition of an excess of any of the basic substances involved in the reaction. Only those substances that increase the concentration of thrombin or supply a thrombin-like element serve to increase the speed of blood coagulation.

According to Morawitz, the present generally accepted hypothesis of the mechanism of blood coagulation is based on the following reactions:

1. Prothrombin + thromboplastin + calcium → thrombin
2. Thrombin + fibrinogen → fibrin

Thromboplastin. The addition of thromboplastin to blood will shorten the clotting time. Until a certain limit is reached, the decrease in coagulation time is proportional to the concentration of thromboplastin. This is due to the more rapid conversion of prothrombin to thrombin. When all of the prothrombin has been converted to thrombin, the addition of further thromboplastin will not shorten the coagulation time.

Calcium. According to Crane and Sanford,[3] the concentration of calcium in whole blood may be varied between wide limits without altering the coagulation time. Aggeler and Lucia[1,9] have demonstrated an optimum concentration for the recalcification of oxalated plasma. The salutary effect of calcium in obstructive jaundice is not due to any direct effect of calcium on the blood-coagulation mechanism but may be due to improvement in the function of the liver.

Prothrombin. Quick[12] showed that the coagulation time of prothrombin-deficient plasma (when thromboplastin is present in excess) is prolonged in proportion to the degree of prothrombin deficiency. The addition of prothrombin to prothrombin-deficient plasma will restore the prolonged coagulation time to normal.

Fibrinogen. Mills[10] advanced the following hypothesis of the mechanism of blood coagulation in wounds: Blood fibrinogen + calcium + tissue fibrinogen → fibrin. This work has, however, not been substantiated.[6] Smith and his co-workers,[13] Davison[4] and Quick[11] working with solutions of *purified* tissue fibrinogen could not verify Mills' conclusions. According to the literature, the source and concentration of fibrinogen have little influence on the clotting time. In its effect on blood coagulation, there is no essential difference between blood fibrinogen and tissue fibrinogen. The addition of purified fibrinogen to normal plasma does not increase the speed of coagulation.

The addition to blood of different varieties of snake venom will shorten the coagulation time. Eagle[5] has shown that the coagulative action of these venoms is probably due to their content of proteolytic enzymes. Some of these enzymes convert prothrombin to thrombin, and some convert fibrinogen to fibrin. Some types of venoms contain both enzymes.

Material Studied. The coagulative potency of 17 commercially available products for hastening the process of blood coagulation was tested. These included two varieties of snake venom, five thromboplastin solutions for local or oral administration, five thromboplastin solutions for hypodermic use, one tissue fibrinogen solution for oral use, one tissue fibrinogen solution for hypodermic use, one substance derived from bovine blood for oral, local or hypodermic use, and two types of refined horse serum for hypodermic use.

The two venoms studied were the Fer-de-lance (*Bothrops atrox*) and Russell viper (*Daboia russellii*). The Fer-de-lance venom is dispensed as a 1 to 5000 solution. The Russell viper venom is dispensed as a powder, 0.1 mg., to which is added 1 cc. of solvent, resulting in a 1 to 10,000 solution.

The five thromboplastin solutions were derived from bovine brain. Those intended for local or oral use are made by the method of Hess,[8] slightly modified. They consist of tissue fluids containing finely ground particles suspended in physiologic saline. The thromboplastin solutions for hypodermic administration are made by dilution, after removal of coagulated proteins and particulate matter, of the material used in the preparation of the local or oral product.

Both the tissue fibrinogen preparation for oral use, and that for hypodermic administration are stated to contain 0.5% cephalin and 1.5% tissue fibrinogen, and are derived from beef lung.

The bovine blood derivative is made by a complicated process of extraction with lipoid solvents. It is stated to contain "certain natural coagulating elements necessary for clotting the blood."

The coagulative action of the two types of horse serum is stated to depend upon the content of thromboplastin. Both have been concentrated and refined so as to reduce their protein content. "The protein has been totally removed" from Product 16, and the potency of Product 17 has been "enhanced by the addition of bovine testicular extract."

For comparative purposes and tests, solutions of thromboplastin similar to those recommended for local, oral and hypodermic use were made from fresh sheep, rabbit, dog, horse and guinea-pig brain.

Method. The choice of a test plasma is of paramount importance. Quick[11] has shown that thromboplastin is, to some extent, specific for the species. Tissue extract of one species, when added to the blood of another species, may show only slight thromboplastic potency; conversely, the blood of one species may respond to a lesser degree to tissue extracts of other species. Preparations of thromboplastin are less active in human plasma than in the plasma of common laboratory animals. Since these agents

are intended for use in human subjects, the only valid test of their potency must be the degree of their activity in human blood. It is of no practical significance that a product will shorten the coagulation time of rabbit blood from 15 minutes to 15 seconds if it has little or no potency in human blood. In all of these experiments, human plasma has been used, and this fact may account partly for the great discrepancy between our findings and the claims made by the manufacturers of these products.

All tests were completed within 1 hour after the blood was withdrawn. It is essential that this time limit be observed, since there is a variable and marked prolongation of the coagulation time when plasma has been allowed to stand longer. The test materials were kept at 0° C. until used. The precautions of Hanzlik and Weidenthal[7] were observed. Testing materials were discarded within 8 hours after the packages were opened. All test materials used were well within their stated expiration dates. Contrary to the observations of Quick[11] and Hanzlik and Weidenthal,[7] Aggeler and Lucia[1] have demonstrated that an optimum concentration of thromboplastin solution is required in order to induce a maximum shortening of the coagulation time of the plasma. For this reason we studied all the products throughout a wide range of dilution. Specimens of both normal and hemophilic plasma were used. Three samples of each product were tested. Five series of tests of each product were performed with specimens of normal plasma, and two series of tests of each product were performed with specimens of hemophilic plasma. The final results are expressed as the average of each series of tests.

The full strength of each product as dispensed by the manufacturer was diluted by serial half-dilutions down to 1/1024 of the original strength. The dilutions were made with 0.85% NaCl. One-tenth cubic centimeter of each dilution was pipetted into clean 13 by 100 mm. glass tubes. One-tenth cubic centimeter of 0.275% $CaCl_2$ was added to each, and the tubes were placed in a water bath at 37° C. Nine cubic centimeters of blood were withdrawn from the antecubital vein, mixed quickly with 1 cc. of 1.34% sodium oxalate in a test tube and centrifugalized at 2000 r.p.m. for 10 minutes. The supernatant plasma was transferred to a test tube which was placed in the water bath and allowed to stand for 10 minutes before being used in the tests.

One-tenth cubic centimeter of plasma was pipetted into the mixture of hemostatic agent and $CaCl_2$. The tube was agitated thoroughly for 5 seconds and the time of coagulation was noted with a stop watch. The test was performed with each dilution of hemostatic agent in turn. Control tests were performed using only 1/10 cc. 0.85% NaCl in place of the hemostatic agent. In order to obtain a satisfactory degree of accuracy, duplicate readings were made varying in time not more than a few seconds from the originals. Most of the agents studied were employed in such concentrations as to yield, upon dilution, a range of concentrations with optimum activity. The actual concentration showing maximum activity is of much less significance than the degree of activity of a substance when present in the optimum concentration, and the range of dilutions through which that activity is distinctly manifested.

Similar series of tests were performed using hemophilic and heparinized normal whole blood. The coagulation times of the specimens of hemophilic blood ranged from 45 to 55 minutes. The coagulation times of the specimens of normal blood were prolonged to between 45 and 55 minutes by the addition of 1 unit of heparin* to each 2 cc. of blood. To perform the test, 0.1 cc. of a dilution of each hemostatic agent was mixed with 2 cc. of blood, and the coagulation time was determined by the Lee and White method. All tests were performed in a water bath at 37° C. Due

* Connaught Laboratories—1000 units per 1 cc.

to technical difficulties, the same degree of accuracy could not be realized when working with whole blood as when working with plasma. However, sufficient data were accumulated to demonstrate that the trend of the results was similar. Products that were inactive in plasma were inactive likewise in whole blood. Products that showed a high degree of coagulative potency in plasma were capable of reducing the coagulation time of the specimens of whole blood to ½ to 3 minutes.

Results. The ranges of coagulation time for the saline control specimens, with which the following results may be compared, were:

For *normal plasma*, 90 to 120 seconds.

For *hemophilic plasma*, 400 to 500 seconds.

1. *Thromboplastin Solutions for Local and Oral Administration.* Products 1 to 5 inclusive are solutions of thromboplastin for local or oral use. In all instances, in both normal (Fig. 1) and hemophilic

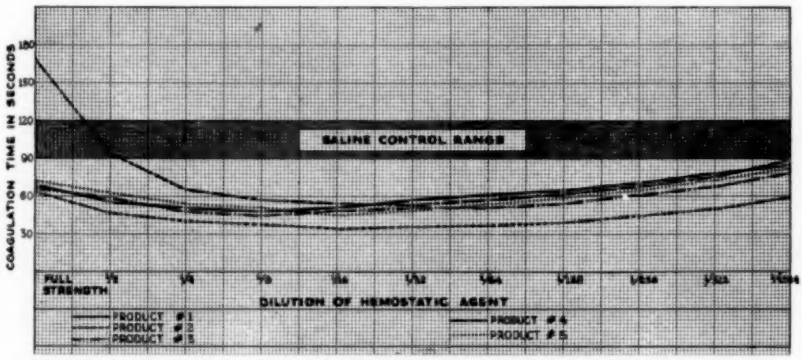

FIG. 1.—The coagulating potency of local thromboplastin solutions tested with normal human plasma.

plasma (Fig. 2), the range of concentrations showing activity was very broad. The shortest coagulation times with *normal plasma* varied between 32 and 52 seconds for the various products. The shortest coagulation times with *hemophilic plasma* varied between 41 and 90 seconds for these same products.

2. *Fibrinogen Solutions for Oral and for Hypodermic Administration.* Products 6 and 9, the preparations of tissue fibrinogen for oral and hypodermic use respectively, were inactive in every concentration in *normal plasma*, and showed only slight potency in high concentrations in *hemophilic plasma*. The coagulation time of the oral product in *hemophilic plasma* was 195 seconds, and of the hypodermic product 120 seconds when the products were used in full strength. Increase in dilution of either product resulted in gradual prolongation of the coagulation time.

3. *Snake Venoms for Local Administration.* (*a*) Fer-de-lance venom. Fer-de-lance venom (Product 7) may be obtained in the dry form as a yellow amorphous substance. It is soluble slowly in

0.85% NaCl and when added to the commercial diluent. It is dispensed commercially as a 1 to 5000 solution, and in this form was found to produce a coagulation time of 47 seconds in the $\frac{1}{4}$ dilution in *normal plasma* (Fig. 4). The coagulation time in *hemophilic plasma* was 57 seconds when the product was used in full strength (Fig. 5). A 1 to 5000 solution of the venom freshly mixed in the commercial diluent in our laboratory gave a coagulation time of 21 seconds in the $\frac{1}{4}$ dilution in *normal plasma*, and of 31 seconds in

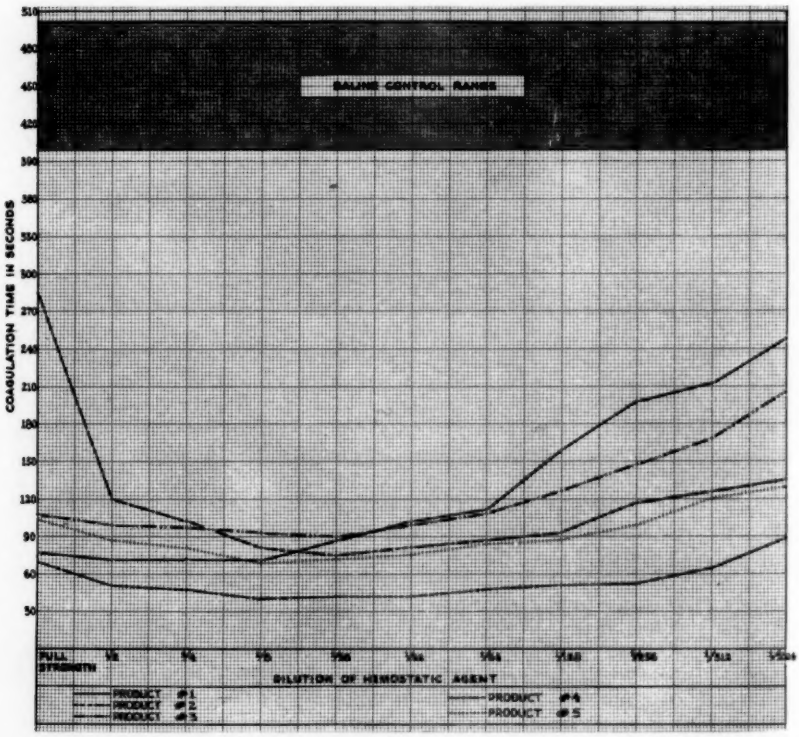

FIG. 2.—The coagulating potency of local thromboplastin solutions tested with hemophilic plasma.

the $\frac{1}{4}$ dilution in *hemophilic plasma*. A 1 to 5000 solution of the venom in 0.85% NaCl in full strength gave a coagulation time of 12 seconds in either *hemophilic or normal plasma*. The commercial diluent in full strength was found to be slightly anticoagulant, prolonging the coagulation time to 170 seconds in *normal plasma*. The anticoagulative action of the commercial diluent and changes due to ageing in solution probably account for the decreased potency of the commercially dispensed solution as compared to venom freshly mixed in 0.85% NaCl.

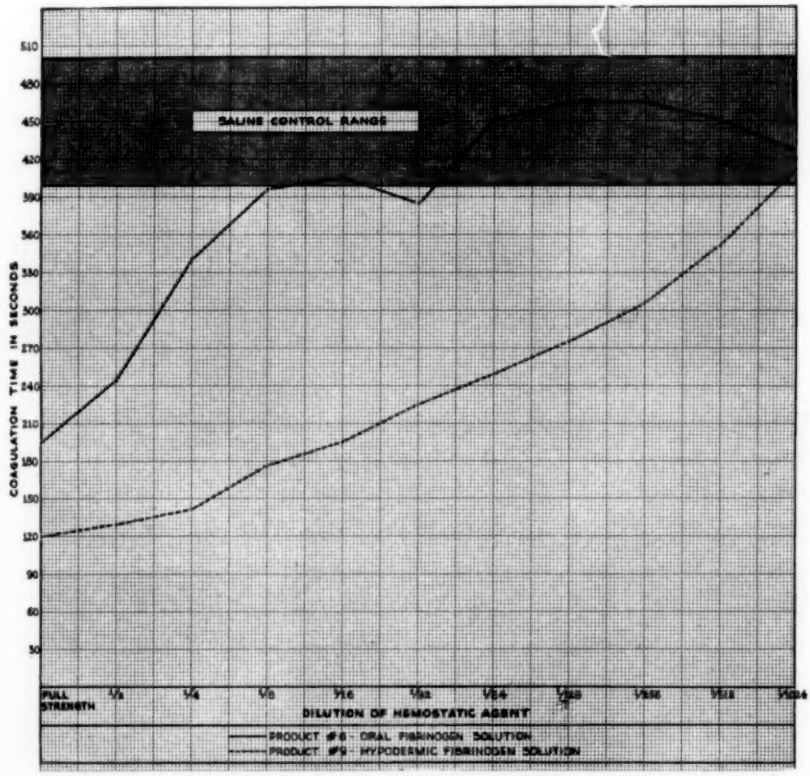
SALINE CONTROL RANGE
COAGULATION TIME IN SECONDS
DILUTION OF HEMOSTATIC AGENT
PRODUCT #6 - ORAL FIBRINOGEN SOLUTION
PRODUCT #9 - HYPODERMIC FIBRINOGEN SOLUTION

FIG. 3.—The coagulating potency of fibrinogen solutions tested with hemophilic plasma.

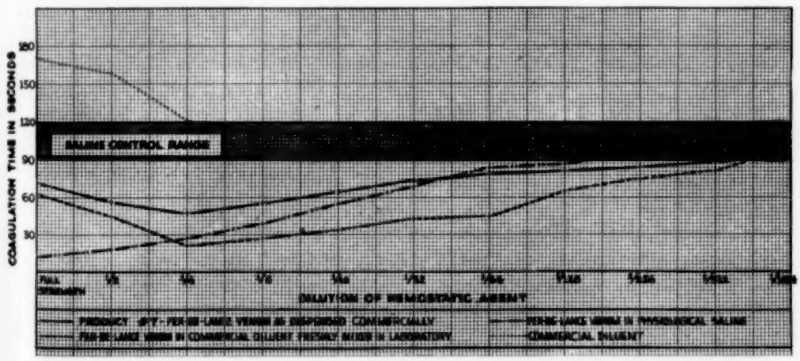

FIG. 4.—The coagulating potency of Fer-de-lance venom tested with normal human plasma.

(*b*) Russell's viper venom. Dried Russell's viper venom (Product 8) is readily soluble both in the commercial diluent and in 0.85% NaCl. Parallel tests with either diluent gave almost identical results. When the product was used in full strength, the coagulation time was 30 seconds in both *normal and hemophilic plasma* (Figs. 6 and 7). In both instances the range of concentrations producing activity was broad.

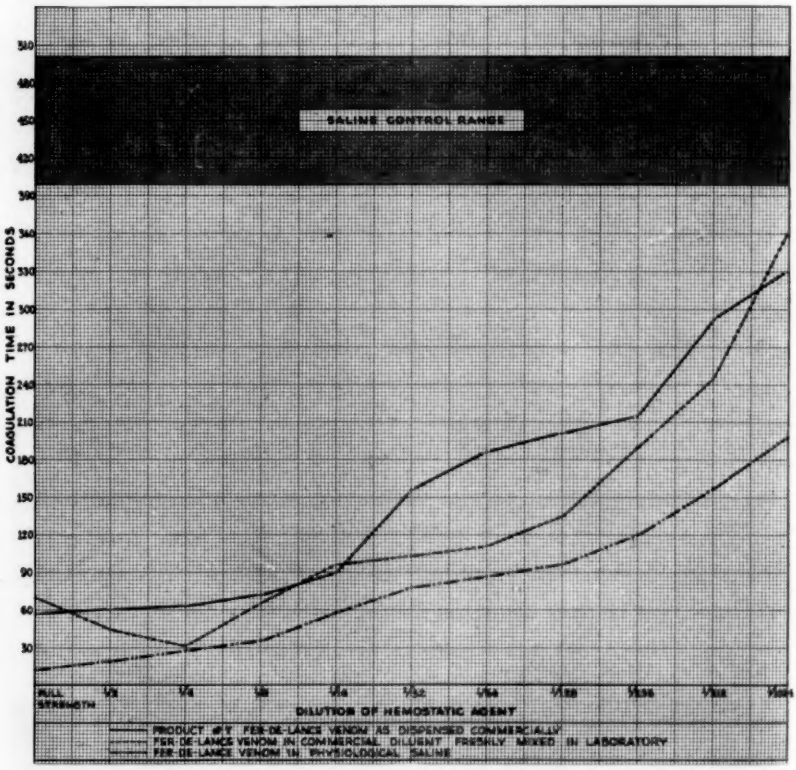
SALINE CONTROL RANGE
COAGULATION TIME IN SECONDS
DILUTION OF HEMOSTATIC AGENT
PRODUCT #7 FER-DE-LANCE VENOM AS DISPENSED COMMERCIALLY
FER-DE-LANCE VENOM IN COMMERCIAL DILUENT FRESHLY MIXED IN LABORATORY
FER-DE-LANCE VENOM IN PHYSIOLOGICAL SALINE

FIG. 5.—The coagulating potency of Fer-de-lance venom tested with hemophilic plasma.

4. *Solutions of Thromboplastin for Hypodermic Administration.* Products 11 to 14 inclusive are either clear, colorless solutions or turbid colloidal suspensions containing a small amount of finely dispersed particulate matter. All of these products were found to be inactive in *normal plasma*. Products 11 and 13 were studied also in *hemophilic plasma* and found to be inactive. Product 10 is a turbid colloidal suspension containing gross tissue particles. It was found to produce a coagulation time of 54 seconds in the $\frac{1}{4}$ and $\frac{1}{8}$ dilutions in *normal plasma*, and of 64 seconds in *hemophilic plasma*.

5. *Bovine Blood Derivative for Local, Oral or Hypodermic Administration.* There was no coagulative activity in any concentration of this product (No. 15) when used either in *normal or hemophilic plasma.*

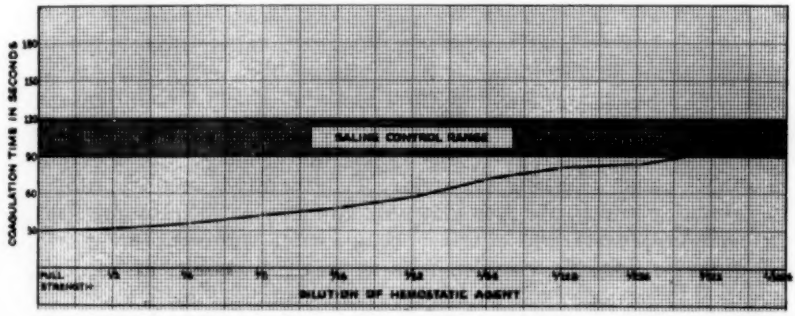

FIG. 6.—The coagulating potency of Russell viper venom tested with normal human plasma.

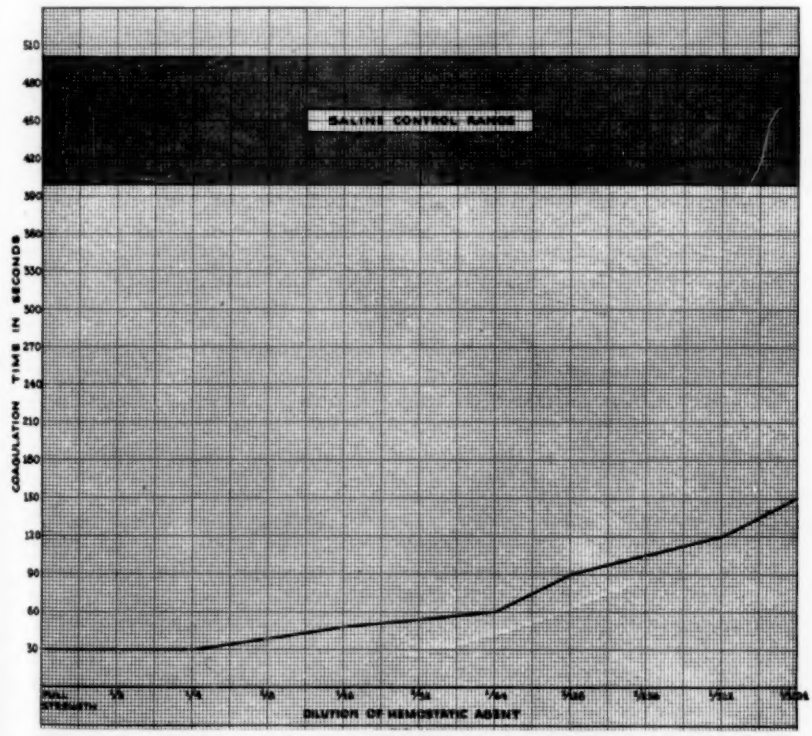

FIG. 7.—The coagulating potency of Russell viper venom tested with hemophilic plasma.

6. *Horse Sera.* These sera, Products 16 and 17, were inactive in *normal plasma.* The effect of Product 17 on *hemophilic plasma* was studied. There was slight coagulative activity in high concentrations when used in full strength, giving a coagulation time of 154 seconds.

7. *Solutions of Thromboplastin for Local Use Derived From the Brains of a Variety of Species.* Local solutions of thromboplastin derived from the brains of the horse, dog, rabbit, sheep and guinea-pig were made by the manufacturer of Product 2 (a thromboplastin solution for local use derived from calf brain). The shortest coagulation times in *normal plasma* for the various products were as follows: horse, 24 seconds; dog, 25 seconds; calf, 34 seconds; rabbit, 37 seconds; sheep, 90 seconds; and guinea-pig, 113 seconds. In *hemophilic plasma* the shortest coagulation times were: horse, 26 seconds; dog, 29 seconds; calf, 41 seconds; rabbit, 36 seconds; sheep, 135 seconds; and guinea-pig, 395 seconds (Figs. 8 and 9).

The products derived from horse, dog, calf and rabbit brain maintained their coagulative activity throughout a very wide range of concentrations. The solutions derived from sheep and guinea-pig brains were highly anticoagulative in high concentrations, and in no concentration was any coagulative activity demonstrable in *normal plasma.* In *hemophilic plasma,* the product derived from sheep brain, upon dilution, showed moderate coagulative activity, while that derived from guinea-pig was inactive.

8. *Solutions of Thromboplastin for Hypodermic Use Derived From the Brains of a Variety of Species.* Hypodermic thromboplastin solutions derived from the brains of the horse, dog, rabbit, sheep and guinea-pig were made by the manufacturer of Product 12 (a solution of thromboplastin for hypodermic use derived from calf brain). These solutions were uniformly inactive in both *normal and hemophilic plasma.*

Comment. All of the commercial solutions of thromboplastin for local or oral use are made from bovine brain. They all possess a high degree of coagulative potency. However, in view of our findings, it is apparent that the brain of the dog or horse is a better source of material for this type of preparation. The solutions of thromboplastin suitable for hypodermic administration are uniformly inactive. It is stated that these solutions are produced by dilution, filtration and deproteinization of the crude material used in the preparation of solutions of thromboplastin for local use. Contrary to the popular conception, this is not a concentration or extraction of the active coagulative elements contained in the crude emulsions. It is possible, by centrifugalization of crude tissue emulsions, to obtain turbid colloidal suspensions free of particulate matter that are as active through as wide a range of concentrations as are the crude tissue emulsions. It is as yet impossible, however, to extract, concentrate or refine the active component contained in these solutions.

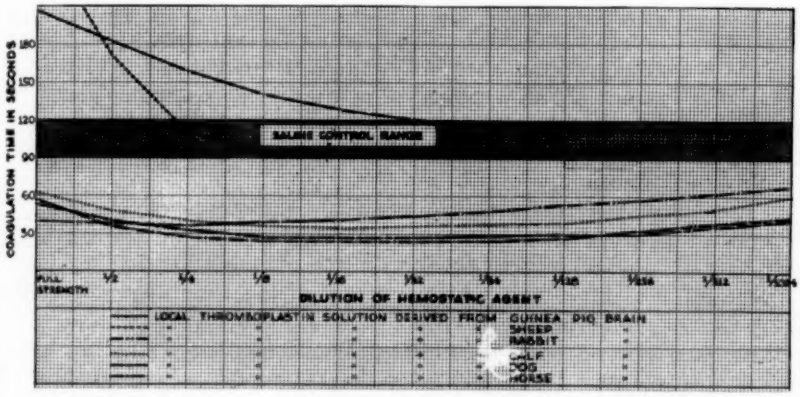

FIG. 8.—The coagulating potency of local thromboplastin solutions derived from the brains of a variety of species tested with normal human plasma.

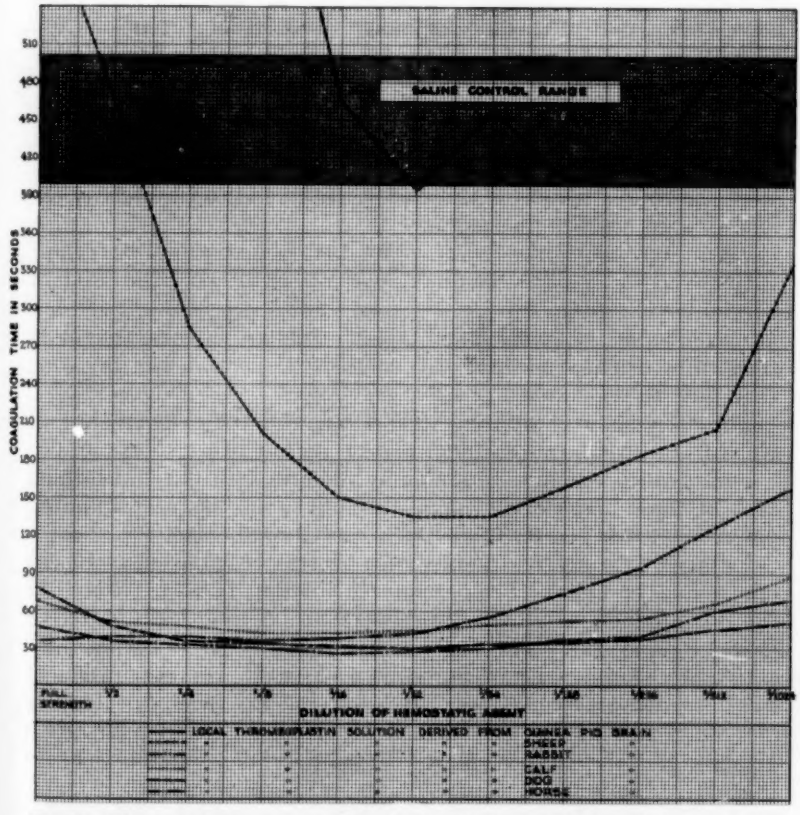

FIG. 9.—The coagulating potency of local thromboplastin solutions derived from the brains of a variety of species tested with hemophilic plasma.

Quick[11] has shown that the coagulative potency of both the extracted material and the residue after extraction with lipoid solvents is markedly diminished. For this reason cephalin, which is an ether extract of brain tissue, is inferior as a coagulant to the crude aqueous emulsion of brain. Recently Chargaff[2] has prepared a highly anticoagulative substance from brain tissue by extraction with lipoid solvents.

The fibrinogen products are relatively impotent. They must depend for their action upon a small amount of cephalin and traces of thromboplastin carried down with the globulin fraction in the preparation of fibrinogen. Fibrinogen itself has been shown to be inactive in promoting blood coagulation. Similarly, the content of thromboplastin in the two sera above mentioned is too small to be of any significance in promoting blood coagulation. The derivative of bovine blood, although it is stated to be an extract of platelets, retains none of the coagulative properties of platelets. It is totally inactive. With respect to all of these products derived from blood or tissue, it is of no intrinsic value whether the material be derived from brain, from lung, from testicular tissue, from serum, or from whole blood. The degree of its ability to supply a coagulative principle is of paramount importance.

The two snake venoms possess a degree of coagulative activity roughly comparable to that of the solutions of thromboplastin for local use.

Of the claims made for the various products, those such as the following are frankly misleading:

Fibrinogen solution: "The clotting time is reduced 90 per cent."

Horse serum: "The coagulant potency is fifteen times that of normal horse serum."

Thromboplastin solution: "(It) is standardized to coagulate citrated or oxalated plasma in two minutes or less, a clotting time very close to the shortest possible reaction."

Thromboplastin solution: "(It) accelerates the clotting time of blood from three to seven times more than any other substance."

Fer-de-lance venom: "Judging by the greatest dilution in which each of these materials is equally effective, (it) has a coagulating power 500 times greater than 10 per cent thromboplastin."

In order to state that a substance hastens coagulation of blood, one should be able to demonstrate this action *in vitro*. Yet 9 of the 17 products studied were found to be practically inactive (Figs. 10 and 11). The only substances that were significantly active were crude tissue emulsions and snake venoms, products suitable exclusively for local or oral use. Products suitable for parenteral administration had no significant potency. In 1919 Hanzlik and Weidenthal showed that Products 15 and 17 had no coagulative action, yet these products are still manufactured and used. The need for potent hemostatics is recognized. The use of

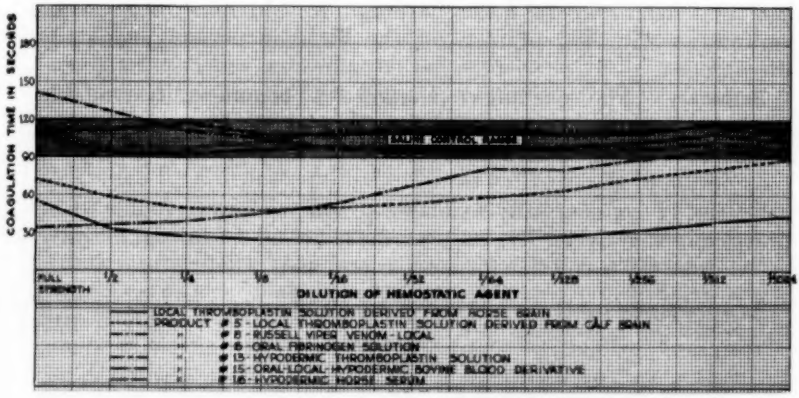
COAGULATION TIME IN SECONDS
SALINE CONTROL BLANK
FULL STRENGTH
DILUTION OF HEMOSTATIC AGENT
LOCAL THROMBOPLASTIN SOLUTION DERIVED FROM HORSE BRAIN
PRODUCT # 5 - LOCAL THROMBOPLASTIN SOLUTION DERIVED FROM CALF BRAIN
8 - RUSSELL VIPER VENOM - LOCAL
6 - ORAL FIBRINOGEN SOLUTION
15 - HYPODERMIC THROMBOPLASTIN SOLUTION
16 - ORAL-LOCAL-HYPODERMIC BOVINE BLOOD DERIVATIVE
17 - HYPODERMIC HORSE SERUM

FIG. 10.—The coagulating potency of various types of commercial hemostatic agents tested with normal human plasma.

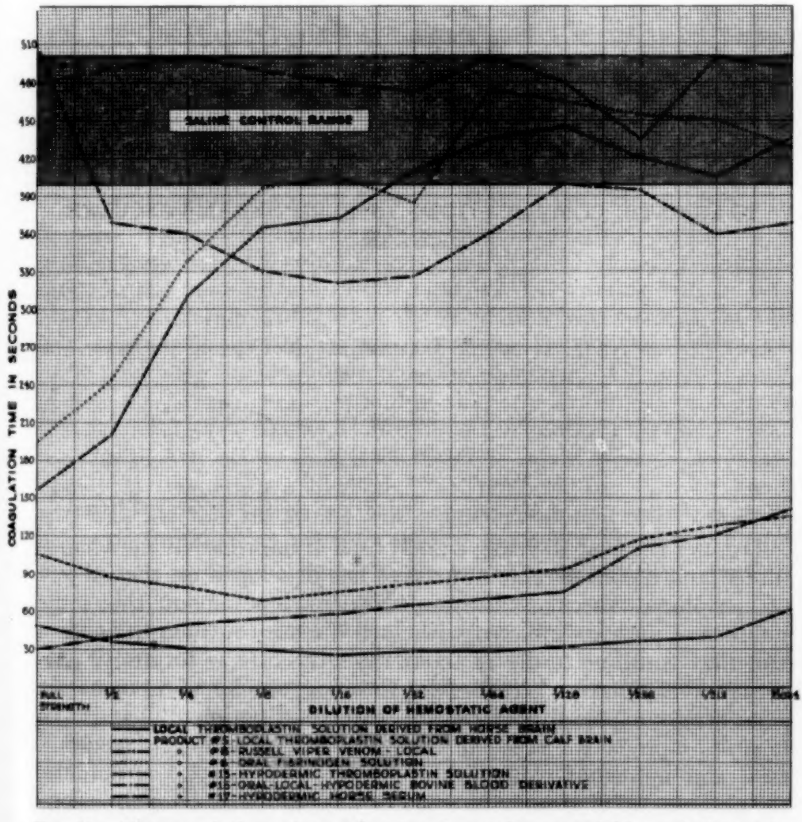
COAGULATION TIME IN SECONDS
SALINE CONTROL BLANK
FULL STRENGTH
DILUTION OF HEMOSTATIC AGENT
LOCAL THROMBOPLASTIN SOLUTION DERIVED FROM HORSE BRAIN
PRODUCT # 5 - LOCAL THROMBOPLASTIN SOLUTION DERIVED FROM CALF BRAIN
8 - RUSSELL VIPER VENOM - LOCAL
6 - ORAL FIBRINOGEN SOLUTION
15 - HYPODERMIC THROMBOPLASTIN SOLUTION
16 - ORAL-LOCAL-HYPODERMIC BOVINE BLOOD DERIVATIVE
17 - HYPODERMIC HORSE SERUM

FIG. 11.—The coagulating potency of various types of commercial hemostatic agents tested with hemophilic plasma.

impotent agents in the forlorn attempt to "do something" when confronted with the problem of the bleeding patient should be discouraged.

Summary. The coagulative potency of 17 commercially available products and of 10 solutions of thromboplastin obtained from the brains of various species were tested for their ability to hasten coagulation of the blood *in vitro*.

Of the 17 commercially available products, 9 were found to be practically inactive. The only products found to be significantly active were those suitable for local or oral use.

We acknowledge indebtedness to various manufacturers for generous supplies of the products used in this study.

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TRAUMATIC COMPLICATIONS IN PERIPHERAL VASCULAR DISEASE.

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During the past 15 years, a great fund of information has accumulated and a considerable awareness has developed on the subject of peripheral vascular disease. Nevertheless, about the same number of patients afflicted with such disease continue to be seen and they continue to die at about the same rate as formerly. Although this situation is rather discouraging, one hopeful but as yet superficially explored field remains for investigation. That is the field of prophylaxis. It is our purpose to call attention to one practical and immediately applicable aspect of prophylaxis; namely, the elimination of trauma as a factor in production of open lesions in extremities afflicted with reduced circulation. While taking

histories of patients so afflicted we were impressed with the frequency of antecedent injury. A brief review of the altered physiology of extremities with diminished circulation will enable us to understand better what constitutes trauma to them.

The skin of the extremities constitutes about 60% of the body surface in man. Body temperature in the normal subject is mostly controlled by a delicate adjustment of circulation to this large skin surface in response to variations of internal and environmental temperatures. This mechanism is the familiar one of vaso-constriction in response to cold and vasodilatation in response to heat. Moreover, as a corollary to circulatory regulation of body temperature an efficient circulation has two other functions: in cold environments it warms the tissues of the limbs; in high environmental temperatures, on the other hand, it acts as a cooling system for these parts in essentially the same manner as does the cooling system of an automobile engine. But the striking result of occlusive arterial disease is to produce a relatively rigid, non-labile circulation. Such an impaired blood flow obviously cannot maintain coolness in relatively high temperatures and cannot maintain adequate warmth in low temperatures. Consequently excesses of cold or of heat easily handled by a normal circulation may be lethal to tissue of an extremity afflicted with a rigid circulation. Hence the frequency in such extremities of frost-bite from mild exposure to cold and of burns from ordinarily harmless therapeutic heat.

A simple experiment will illustrate this point. The subject was a male Greek of 53 suffering from thrombo-angiitis obliterans of both extremities. He complained of pain in the feet at night and of intermittent claudication in the right calf on walking four or five blocks. Moderate diminution of circulation was present on the left; marked diminution on the right (Fig. 1). In the experiment both feet were enclosed in a heating chamber. Observations of environmental temperatures and of skin temperatures of the great toes were taken at intervals. At room temperature the right great toe was slightly cooler than the left as one would expect. As environmental temperature increased the temperature of both great toes rose together for a time, but later the temperature of the right great toe suddenly rose above that of the left. At the end of 50 minutes in an environmental temperature of only 104° F. pain in the right foot necessitated ending the test.

Another point in regard to heat should be understood. Freeman[3,4] has shown that temperatures above normal in the extremities increase local tissue metabolism. In other words, warmed tissues require increased circulation to bring more oxygen and food and they produce more waste products to be carried away. But a rigid circulation can not meet such a demand. Consequently, heat accelerates death of tissue poorly supplied with blood. It is not strange, therefore, that ordinary therapeutic heat, so successfully

used for various aches and pains and for inflammatory processes in normal individuals, may result in serious burns and rapid extension of necrosis when employed on patients with obliterative vas-

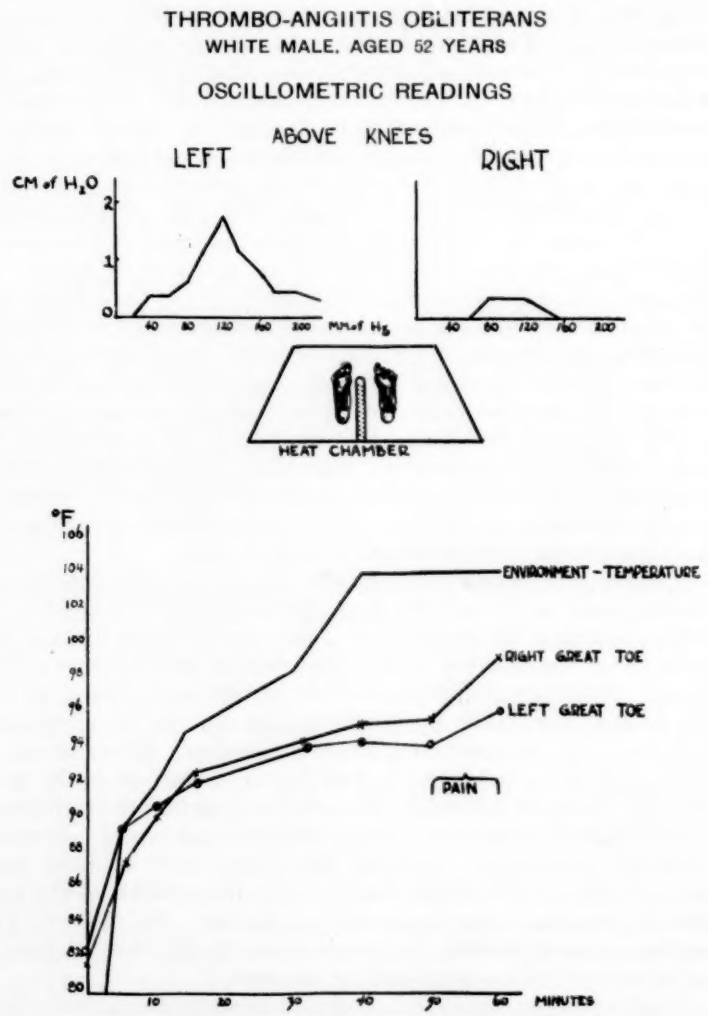

FIG. 1.—Effects of high environmental temperatures on extremities with normal and with diminished arterial circulation.

cular disease. An inflammatory process also increases local metabolism, which accounts for the rapidly advancing gangrene frequently seen when an inflammatory process involves a poorly nourished extremity.

The increased vulnerability of limbs with deficient circulation is further increased by the rapid loss of function of completely or relatively ischemic sensory nerves.[7] Persons with ischemic extremities are very apt to be unaware of temperature excesses which are producing injury. It is not unusual for patients using hot soaks of feet and legs to relieve the pain due to limited circulation to sustain severe burns without experiencing the pain which usually occurs with such burning.

In résumé, physiologic responses to thermal stimuli are altered in three ways in ischemic limbs: the warming and cooling functions of the circulation are impaired; capacity to cope with increased metabolism of warmed or inflamed tissues is diminished; sensibility to painful stimuli is lessened.

Consider mechanical types of injury. It suffices to mention such accidental injuries as stubbing the toe and bruising or crushing a toe or foot. The onset of many open lesions begin with a blister or a corn raised by tight or ill fitting shoes. In a large number of patients open lesions follow a visit to a chiropodist or to a physician for treatment of corns and of real or alleged ingrowing toenails. Pressure is also a frequent source of injury. In the words of Sir Thomas Lewis,[7] "Much lower pressure than that required to collapse the main artery will, when exerted directly upon the muscle itself, collapse its capillaries and completely arrest the blood flow to it. A pressure of 50 or 60 mm. Hg upon skin is known to stop all blood flow to it." He further states that ischemic muscle dies in 6 to 8 hours, nerve in 12 to 20 hours and skin in 24 to 36 hours. One can readily understand why relatively minor degrees of pressure on poorly nourished extremities may produce rapid and extensive necrosis.

Even improper position of the limb may be injurious. Reid[10] showed that optimum circulation occurs in an extremity resting 6 or 8 inches below the heart's level. Yet most patients are advised to elevate their legs on several pillows. The patient, on the other hand, in his attempt to escape from pain is frequently seen with a cold blue foot hanging out of bed.

Strong chemicals frequently injure undernourished extremities. Chemicals powerful enough to act as germicides may be equally deadly to devitalized tissue. Because circulation in these limbs is usually not adequate to sustain an inflammatory process, application of chemicals to produce counter-irritation, essentially an inflammatory process, is dangerous. Chemicals such as iodine, salicylic acid, phenol and other germicides and counter irritants should be used with great caution in peripheral vascular disease.

Clinical Material. Tables 1 and 2 present clinical data on 40 patients who were admitted to the hospital for peripheral vascular disease during a 6-month period. That such patients constitute a serious medical and economic problem is attested by the following

facts. In a hospital in which the average patient's stay is 12 days, these averaged 55 days. Based on the United Hospital Fund (New York) the average cost for each patient was $303; $12,122 for the group. Moreover, during the same period in which 40 patients were admitted for peripheral vascular disease, only 9 were admitted for perforated peptic and duodenal ulcers and only 33 were operated for gall bladder disease. Furthermore, of 52 patients with peripheral vascular disease who entered with open lesions more than half required amputation and more than half of those having amputa-

TABLE 1.—PATIENTS ADMITTED PRIMARILY FOR PERIPHERAL VASCULAR DISEASE, FEBRUARY 1 TO AUGUST 1, 1938.

Male 31 Female 9 Total 40

Age distribution:						
Decade	3d	4th	5th	6th	7th	8th
Male	1	1	4	9	12	4
Female		1	2	1	3	2
Total	1	2	6	10	15	6

Diseases:	
Thromboangiitis obliterans	7
Occlusive arteriosclerosis	10
Occlusive arteriosclerosis with diabetes	19
Arterial embolus	4

Mortality:	No.	Per cent.
Patients who entered the hospital with open lesions	32	
Amputations on these patients	17	53
Deaths following amputation	9	53
Deaths not following surgery	1	
Total deaths in 40 patients	10	25
Deaths in those who entered with open lesions	10	31

tions died. In other words, a person afflicted with peripheral vascular disease, who develops an open lesion, is immediately faced with a prolonged and painful disability and about a 30% chance of dying. These figures agree closely with those of other writers.[6] Even if these patients survive amputation, only about 10% are ever economically rehabilitated.[6] Obviously development of open lesions in vascular disease of the extremities is an occurrence of dire import.

Table 2 shows that trauma is apparently a major factor in production and aggravation of open lesions. Of 32 patients from whom a satisfactory history was obtainable more than half of them had sustained one or more types of injury. The majority of these injuries resulted from some form of ill-advised therapy. That injury, as well as diminished circulation, is often necessary to produce open lesions is indicated by the fact that in 13 of these patients circulation was equally poor in both extremities and that in 7 the lesion was actually on the limb with distinctly better circulation. There were 37 instances of injury in 21 patients. In only 13 instances was self treatment or an accident the source of injury. The remain-

ing 24 instances of trauma occurred through the advice or at the hands of some professional attendant; 53% of the injuries were occasioned by medical attendants.

TABLE 2.—TRAUMA.

		No.	Per cent.
History of trauma		21	52
No history of trauma		11	27
Unsatisfactory history		8	20
		40	
Lesions:			
Gangrene		20	
Dry	11		
Infected	9		
Indolent ulcer		7	
Cellulitis or osteomyelitis		5	
Total with open lesions		32	
No open lesions		8	
Syphilitic		6	
Site of lesions:*			
Lesion on extremity with poorer circulation		12	
Lesion on extremity with better circulation		7	
Circulation of both extremities essentially same		13	
Those responsible for the trauma:			
Patient		13	35
Chiropodist		4	11
Family physician		18	48
Hospital staff		2	5
		37	

Types of injury:

1. *Mechanical:* 17 instances.
   - A. Pressure.
     1. Tight shoes.
     2. Casts applied for "arthritis," "varicose veins," etc.
     3. Pressure of heel on bed with resulting gangrene.
   - B. Local operations on corns or nails.
   - C. Accidental injuries such as stubbing toe or having it stepped on.
2. *Thermal:* 16 instances.
   - A. Cold. Usually exposure. Occasionally, too enthusiastic use of contrast baths.
   - B. Hot soaks. Usually in strong solutions of Epsom salts ("as hot as you can stand it").
   - C. Baking lamps and infra red lamps.
   - D. Diathermy and short wave.
3. *Chemical:* 4 instances. Iodine, salicylic acid and phenol ointments. Vaseline gauze to dry gangrene. Use of strong chemicals for epidermaphytosis.

* Measured by exercise and blanching test, venous filling time, oscillometry and histamine readings.[1,2,5,9,11a,b]

Discussion. The idea unfortunately still persists that specialized knowledge and considerable elaborate and expensive apparatus are required for diagnosis of vascular diseases of the extremities. The contrary, however, is true. In a previous publication[8] one of us showed that accurate diagnosis of circulatory status can be made at the bedside without apparatus of any kind and with only the familiar methods of inspection and palpation and two simple tests.[1,11b]

Failure to recognize deficiency of circulation is often the starting point of mischief. Accurate diagnosis and early recognition of the vulnerability to trauma of these patients is their best safeguard. Having recognized diminished circulation of the extremities the physician must keep clearly in mind those measures to be avoided and those to be carried out to prevent onset of open lesions. Properly fitting shoes, light woolen socks, scrupulous cleansing of the feet with tepid water and non-caustic soap, gentle drying with soft towels; avoidance of cold and wet, meticulous care of the nails, corns and callouses, adequate rest, supervised exercise and the general medical measures especially adapted to the case—all these are requisite. Indiscriminate applications of wet dressings, whether hot or cold, use of moist or dry heat and employment of strong chemicals cannot be tolerated. Avoid pressure on the heel and pressure on the popliteal space by bunched-up pillows. Pressure from bed clothes should be eliminated. Body temperature of the limb may best be maintained by warm clothing and by wrapping the entire foot and leg loosely in cotton wool. Contrast baths may do more harm than good. Dry dressings or none at all are usually preferable. Maceration of tissue by vaseline gauze or by other occlusive dressing should be avoided.

Surgical trauma, likewise, should be reduced to a minimum. Surgery, when indicated, must not be delayed and it must be adequate. Radical surgery is usually the most conservative, because few of these patients can tolerate repeated surgical insults, whereas many will survive a single, well planned attack. If amputation is necessary, it should be performed at a level at which risk of contamination is least and at which viability of tissue is most promising. Scrupulous skin sterilization, careful draping, elimination of tourniquets, clean quick incisions with sharp scalpels without bevelling skin edges, gentle retraction, no clamping of skin, no interruption of essential blood supply by separation of skin from underlying tissue in fashioning flaps, nice hemostasis without gross clamping of tissue, fine ligatures throughout except where heavier material is essential, no suturing of muscle, judicious apposition of fascial edges, accurate closing of skin without tension and finally, a well applied dressing without drainage—all are requisite. Such precautions entail a minimum of operative trauma. The operative site may usually be forgotten until healing has occurred. Even after amputation the remaining limbs of these patients are still subject to the effects of trauma and must be carefully safeguarded.

Summary and Conclusions. 1. Because of the altered physiology of extremities afflicted with obliterating arterial diseases many ordinary therapeutic measures cause injury and produce open lesions in such limbs.

2. Investigation of 40 patients with peripheral vascular disease showed that more than half of them suffered one or more injuries in the course of ill advised attempts at treatment.

3. Trauma appears to be the most frequent cause of open lesions in extremities with poor arterial blood supply. Types of injury have been discussed.

4. Because development of open lesions on poorly nourished limbs entails great economic loss, prolonged morbidity and a high death rate, every effort should be made to eliminate trauma in patients with peripheral vascular disease.

5. This object can be accomplished only by a widespread and a persistent campaign of education among physicians.

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ELECTROCARDIOGRAPHIC STUDIES IN METRAZOL SHOCK THERAPY.

REPORT OF ELECTROCARDIOGRAPHIC FINDINGS OBTAINED IN THE TREATMENT OF 50 SCHIZOPHRENIC PATIENTS WITH CONVULSIVE SHOCK INDUCED BY METRAZOL.

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SINCE the introduction of metrazol shock therapy in the field of the functional psychoses, much attention has been devoted to the changes in the bodily economy induced by the large doses of this potent drug which are required to produce the therapeutically desired grand mal seizures. Particularly thoughtful workers have been concerned with the possibility of serious or even fatal damage to the brain, heart, lungs, kidneys, skeletal structures, and so on, as a result of this therapy.

That disastrous effects[2,3] on the cardiovascular system can follow the incautious administration of this drastic therapy, there is little doubt. Thus, von Angyal and Gyarfas[1] record a fatal case in which

aortic stenosis was found to be present at postmortem. Hayman and Brody[4] also report a fatal case in which a preëxistent chronic endocarditis was found at autopsy.

Such instances emphasize the danger of convulsive doses of metrazol in patients with damaged hearts. This paper is the outgrowth of an effort to determine the possible untoward effects of metrazol shock therapy upon the cardiovascular system of young subjects manifesting no evidence of impaired cardiovascular system before the institution of therapy. In particular, we are concerned here with such possible ill effects insofar as they can be detected by electrocardiographic studies.[7,8] Collateral phenomena such as roentgenologic studies of the cardiovascular system, blood pressure, venous pressure, and so on, are not included in this report.

Material and Method. The material for this work was taken from electrocardiographic studies on schizophrenic subjects undergoing metrazol shock therapy at this hospital. All patients considered for this treatment underwent as routine work-up a careful clinical examination of the cardiovascular system, Roentgen ray of the chest and an electrocardiogram besides the other usual tests. In addition, each patient received at the conclusion of the therapy a clinical check-up of the cardiovascular status and a second electrocardiogram.

Patients selected for this study were all diagnosed as suffering from schizophrenia. There were 25 males and 25 females in the present series of 50 patients. The oldest patient was 44; the youngest 19 years (average age, 26 years). Patients presenting any cardiovascular abnormalities either on clinical, roentgenologic, or electrocardiographic examination were considered unsuitable for therapy and hence excluded from this study. Treatment consisted of intravenous injections of 10% aqueous solution of metrazol (pentamethylenetetrazol) 3 times a week according to the technique developed by von Meduna.[6] The duration of therapy lasted from 4 to 16 weeks (average, 8 weeks). The total amount of metrazol solution injected was from 64 to 469 cc. (average, 196 cc.). The number of grand mal seizures varied from 10 to 40 (average, 21).

The electrocardiograms for this study were analyzed for rate and rhythm, *P*, *Q*, *R*, *S*, and *T* waves, *P–R* and *S–T* segments. The electrocardiogram before the institution of therapy was compared with the one taken after the completion of the treatment.

Results. In this series of 100 electrocardiograms (50 before and 50 after treatment), the rhythm in every instance was of a sinus type. Thirty-one (62%) of the cases showed an increase of rate after treatment (3 [6%] of the cases showed a decrease in rate after therapy). Average rate before treatment was 85; after treatment, 115. The increase in rate following therapy was attributed to emotional factors, since it was observed that those patients who manifested nervousness, anxiety, fear and apprehension while the electrocardiogram was being taken frequently showed tachycardia. This has been commonly observed following metrazol shock treatment, since many patients evidently confused the electrocardiogram with the feared metrazol injection.

Apparently related to this phenomenon was the shortening of

the S–T segment (interval) which was observed in 23 (46%) of cases following therapy (as compared with electrocardiogram before treatment). In every instance in which this phenomenon was observed, the rate was found to have increased after therapy. Four of these 23 patients likewise showed a shortened P–R interval. We regard this shortened S–T interval, and occasional shortening of P–R interval, as merely a physiologic concomitant of the increased rate.

There were no significant changes in P waves or QRS complexes in our entire series. The T waves in 48 (96%) of our series likewise showed nothing significant. In 2 patients, however, interesting changes were observed as seen below.

Case 1.—G. M., a 21-year-old female had a negative electrocardiogram before institution of therapy. She received a total of 310 cc. of metrazol given in 40 injections, 30 of which resulted in grand mal seizures. The largest single dose was 9 cc. Her therapy was terminated on March 3, 1939. At no time during or after treatment were any cardiovascular abnormalities detected clinically. However, routine electrocardiogram on March 9, 1939, showed inversion of T_2 and T_3, with depression of S–T_2. The T waves were of cove-plane type and suggested coronary changes. On April 5, 1939, a similar record was obtained. On April 10, 1939, however, without any therapy of any sort, these changes disappeared and a normal electrocardiogram was obtained. Furthermore, electrocardiograms on April 18 and 25, 1939, showed upright T waves in all leads and negative electrocardiograms.

Case 2.—S. L., a 21-year-old male with negative electrocardiogram before therapy was given a total of 189.5 cc. of metrazol in 25 injections. He had 20 seizures of grand mal type. The largest single dose was 10 cc. His last injection was given on April 26, 1939. An electrocardiogram on April 28 revealed inverted T_2 and T_3 and again was considered as suggesting coronary disease. It was suggested that anoxemia[5] might account for these changes. Acting upon this suggestion, the patient was given 100% oxygen by inhalation (with a Gwathmey anesthesia machine) for 15 minutes. Thirty minutes later, an electrocardiogram was taken and revealed that most of the T waves in Leads 2 and 3 were upright. On May 19, 1939, the T waves were still upright and electrocardiogram was normal in appearance.

Summary. 1. Electrocardiographic tracings taken before and after metrazol shock therapy administered to young healthy adults revealed no significant changes of a permanent nature.

2. An increase in heart rate is frequently observed following therapy. This we believe is due to emotional factors rather than to the metrazol injections *per se*. Shortening of S–T (and less commonly of P–R) intervals is also commonly observed. This, in our opinion, is associated with the increased rate.

3. Inversion of T waves in Leads 2 and 3 following therapy occurs in isolated instances. These changes are transient in nature. The mechanism of these changes is somewhat obscure, although they are possibly correlated with anoxemia. This requires further investigation.

4. We wish to emphasize again the need for careful check-up of the physical condition of patients who are being considered for

metrazol therapy. In making such investigations of the physical status of these patients, an electrocardiogram is a valuable adjunct.

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CHLOROFORM LIVER INJURY INCREASES AS PROTEIN STORES DECREASE.

STUDIES IN NITROGEN METABOLISM IN THESE DOGS.

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LIVER injury due to chloroform anesthesia increases in degree as the protein stores are depleted in the liver and body tissues. This is the theme of the experiments tabulated below. Clinicians as well as investigators have a legitimate interest in these observations owing to the unfortunate fact that chloroform is still used as an anesthetic in this country and abroad. If surgeons and obstetricians will persist in the use of this dangerous drug (chloroform) alone or combined with other anesthetics, at least they should realize that the toxicity of chloroform increases as the protein stores are depleted by fasting, intestinal disturbances, bleeding, dietary limitations or even infection.

The normal *well-fed* healthy dog will tolerate an *hour* of surgical chloroform anesthesia with little evidence of severe liver injury. The normal dog *fasted for 3 days* preceding an hour of chloroform anesthesia will always show well marked hyaline central necrosis of the liver, sharp lowering of the fibrinogen and prothrombin levels in the blood, definite increase in bile pigment in blood plasma and urine, large increase in urinary nitrogen and definite clinical intoxication. This is a uniform reaction which can be demonstrated

over and over again, the central liver necrosis involving usually 50 to 70% of the liver cells in each lobule. Occasionally the injury will be severe enough to cause death in 2 to 4 days: "delayed chloroform poisoning."

But when the dog is *depleted of its store of proteins* by long continued low-protein diets with or without bleeding or by plasmapheresis[9] (bleeding and return of washed red cells in saline), we see that the liver is very sensitive to chloroform poisoning (Table 1). These *protein depleted dogs* (normal in all other respects) are scarcely able to tolerate 12 minutes of light chloroform anesthesia and 20 minutes will be fatal in the great majority of cases.

There is every reason to suppose that human beings react like these dogs and under certain conditions may be hypersensitive to chloroform anesthesia. In fact, many cases of fatal chloroform poisoning have been observed and some reported in recent years. In our opinion it would be folly to subject to short chloroform anesthesia human patients who have been vomiting for long periods or who are in a state of inanition due to diet or infection. Young animals and presumably children are somewhat more susceptible than adults.

Methods. All dogs used in these experiments were active, healthy adults. As indicated in detail in the individual protocols, the dogs' reserve stores of protein were depleted by bleeding and diet, or by diet alone, or by plasmapheresis. Before starting these procedures the dogs' plasma protein levels were normal (6 to 6.5 gm.%). The constant drain on body protein stores extending over a period of 4 to 7 weeks, finally results in a lowered plasma protein level. A plasma protein level of 4 to 5 gm.% for at least 1 week before the chloroform anesthesia and throughout the metabolism studies was taken to indicate a rather severe depletion of reserve protein stores.

During the metabolism experiments the dogs were kept in the laboratory in galvanized iron metabolism cages. The urine was collected under toluene and preserved with toluene and refrigeration. Each period of 24 or 48 hours was terminated by catheterization and rinsing of the bladder with water. Urine analyses were made on the specimens of each period for the following constituents: Total nitrogen by macro-Kjeldahl, ammonia and urea nitrogen by aëration after urease treatment, creatine and creatinine by the methods of Folin, and uric acid by the method of Morris and MacLeod. Blood samples were drawn from the external jugular vein with 1.4% sodium oxalate used as anticoagulant. Plasma protein determinations were carried out by macro-Kjeldahl on the whole oxalated plasma without correcting for non-protein nitrogen, fibrinogen was determined by micro-Kjeldahl, and icterus index by comparison of the oxalated plasma with standards prepared according to the method of Farahaugh and Medes.[5]

The animals were maintained on a diet consisting of cane sugar, lard, protein-free butter, bone ash, a salt mixture,[13] cod liver oil, thiamine chloride, and a small amount of protein in the form of a liver extract (Liver extract No. 343*) or 5 to 20 gm. of fresh pork liver daily. The exact composition of the daily diet of each dog is given in detail in the individual protocols. With one exception the dogs were fasted 24 hours before the administration of chloroform. By fasting we mean a discontinuance of food but a liberal supply of water.

* We are indebted to Eli Lilly and Company for a supply of this material.

Anesthesia was induced with ether and then chloroform was given by the drop method. A light surgical anesthesia was maintained. All dogs recovered from the anesthesia quite rapidly and were conscious within 2 to 4 minutes.

Experimental Observations. We believe the tables given below present adequate evidence to establish our thesis that the liver becomes more susceptible to chloroform injury as the protein reserves are depleted. It is generally accepted that the liver is an important organ for the storage of body protein, but other tissues, for example muscle, are probably actively concerned.

Table 1 is a summary table including 6 fatal cases subjected to brief chloroform anesthesia. Plasma protein levels were not very low except in Experiments 2 and 6, but the protein reserve stores were probably low in all 6. Depletion is readily effected by diet or bleeding. In the fatal cases there was a conspicuous drop in blood fibrinogen within 24 hours after the chloroform anesthesia and a sharp rise in the icterus index. At autopsy, the fibrinogen was very low as evidenced by complete lack of blood clots.

Glycine in considerable amounts given in the diet did not protect the dog (Exp. 5, Table 1) nor did xanthine (Exp. 6) given according to the technique used by Neale and Winter.[11]

TABLE 1.—FATAL LIVER INJURY BY CHLOROFORM ANESTHESIA IN PROTEIN-DEPLETED DOGS.

Experiment No.	Dog No.	Protein depletion.		Plasma protein level, gm. %	Duration of anesthesia, min.	Hours between anesthesia and death.	Fibrinogen* 24 hrs. after chloroform, mg. %	Extent of liver necrosis estimated, %
		Method.	Duration, wks.					
1	38–30	Bleeding + Diet	7	4.28	45	15 ±	...	90
2	38–18	Diet	4	3.56	30	56	129	60
3	38–144	Bleeding + Diet	6	4.25	20	60	30	50
4	38–196	Bleeding + Diet	6	4.60	15	31	88	75
5	38–274†	Diet	7	5.15	20	15 ±	...	95
6	38–81‡	Plasmapheresis + Diet	7	3.85	20	65 ±	89	70
7	38–241	Diet	9	4.70	20	...§	590	trace ?

* Blood clots absent at autopsy in each fatal experiment.
† Glycine fails to protect against chloroform liver injury.
‡ Xanthine fails to protect against chloroform liver injury.
§ Single meat feeding gives protection against chloroform liver injury.

A *single protein feeding* in Experiment 7 did prevent completely any liver injury due to 20-minute chloroform anesthesia. Experiment 9 in Table 3 gives support to this important Experiment 7.

More experiments bearing on this point are in progress but these results are so unequivocal as to give some assurance that these single experiments are really significant.

It is of interest to note that the dogs used in these experiments had reserve protein stores of different amounts or conserved these stores over different periods. Dog 38-18 required only 4 weeks of low protein diet, whereas Dog 38-30, with the extra drain of bleeding, required 7 weeks of low protein diet to effect depletion.

The fact that Dogs 38-30, 38-144, and 38-186 were moderately anemic as well as hypoproteinemic at the time of chloroform anesthesia does not appear to have rendered them any more susceptible than the others. It will be recalled that Daft, Robscheit-Robbins and Whipple[1] did not find anemic dogs any more susceptible to chloroform poisoning than normal dogs.

EXPERIMENT 1 (Table 1), Dog 38–30, adult female airedale mongrel.

Oct 4. Initial plasma protein level, 6.88 gm.%. Weight, 16 kg. Started bleeding and low protein diet (sucrose, 138 gm.; lard, 30 gm.; butter, 14 gm.; bone ash, 4 gm.; salt mixture, 2.5 gm.; cod liver oil, 15 gm.; thiamine, 60 I. U.; liver extract, 2.6 gm.) fed daily in afternoon.

Oct. 5. Bleeding and diet continued until start of metabolism study. Plasma protein, 4.54 gm.%. Red cell hematocrit, 31%. Weight, 12.7 kg.

Nov. 26. Plasma protein, 4.16 gm.%. Diet, 30% consumed.

Nov. 27. Diet, 20% consumed.

Nov. 28. Fasted.

Nov. 29. *Chloroform anesthesia 45 minutes.* Recovery uneventful. Refused food offered.

Nov. 30. Dog found dead in morning. Autopsy showed central areas of lobules deep red, portal areas yellowish. Microscopically there was almost complete disappearance of normal liver tissue with about 90% central hyaline necrosis.

EXPERIMENT 2 (Table 1), Dog 38–18, adult female hound mongrel.

Oct. 4. Initial plasma protein level, 6.62 gm.%. Red cell hematocrit, 47%. Weight, 12.5 kg. Low protein diet daily (sugar, 118 gm.; lard, 25.5 gm.; butter, 12 gm.; bone ash, 3.1 gm.; salt mixture, 2.1 gm.; cod liver oil, 15 gm.; liver extract, 2.2 gm.; thiamine, 60 I.U.).

Oct. 31. Plasma protein level, 4.46%. Red cell hematocrit, 42%. Weight, 12.1 kg.

Dec. 2. Since appetite past several days was poor, diet was supplemented hereafter with 15 gm. fresh pork liver. Weight, 11 kg.

Dec. 3, 4. Consumed 60% diet.

Dec. 5. Fasted.

Dec. 6. Plasma protein level, 3.70 gm.%. Red cell hematocrit, 40%. *Chloroform anesthesia 15 minutes.* Recovery rapid. Somewhat intoxicated. Refused food. Only slight rise in total urinary nitrogen and fourfold increase in uric acid, but no icterus and only slight drop in blood fibrinogen. Consumed average of 40% diet on Dec. 7 and 8.

Dec. 9. Fasted.

Dec. 10. *Chloroform anesthesia 30 minutes.* Dog recovered rapidly but later vomited mucus and looked ill.

Dec. 11. Icterus prominent. Fibrinogen, 129 mg.%. Refused food. Clinically intoxicated. Sugar by vein several times (total sugar 50 gm.) and 200 cc. of 5% glucose subcutaneously.

Dec. 12. Icterus very marked. Fibrinogen 80 mg.%. Despite glucose and transfusions dog died. Total urinary nitrogen for Dec. 10 and 11 almost double the control value of 1.2 gm. per 48-hour period. Slight increase in creatine. About sevenfold increase in uric acid. On autopsy grossly, liver appeared to show severe injury. Microscopically, about 60% of each lobule showed the characteristic hyaline necrosis. Many cells appeared stuffed with glycogen.

EXPERIMENT 3 (Table 1), Dog 38–144, adult female hound mongrel.

Jan. 12. Plasma protein level, 6.53 gm.%. Red cell hematocrit, 45%. Started low protein diet and bleeding (sugar, 128 gm.; lard, 27.6 gm.; butter, 13 gm.; bone ash, 3.3 gm.; salt mixture, 2.3 gm.; cod liver oil, 5 gm.; liver extract, 2.4 gm.; thiamine, 60 I.U.). Weight, 12.9 kg.

Jan. 13 to 29. Ate 80 to 90% diet.

Jan. 30. Plasma protein level, 4.58 gm.%. Weight, 11.8 kg.

Feb. 1 to 14. Ate 80 to 90% diet. Weight, 12 kg.

Feb. 15. Fasted.

Feb. 16. Plasma protein level, 4.25 gm.%. Red cell hematocrit, 30%. Fibrinogen, 277 mg.%. *Chloroform anesthesia 20 minutes.* Recovery rapid. Refuses food.

Feb. 17. Icterus pronounced. Fibrinogen 30 mg.%. Very ill. Gave several doses intravenous glucose (total sugar 100 gm.).

Feb. 18. Dog semi-comatose. Despite intravenous glucose and plasma protein dog died. Changes in urinary nitrogen for Feb. 16 and 17 practically same as in Dog 38–18. Autopsy revealed liver lobules which had uniformly deep red central areas, yellowish portal areas. Microscopically, there was at least 50% central necrosis of lobules. Remaining liver cells showed extensive fatty degeneration.

EXPERIMENT 4 (Table 1), Dog 38–186, adult female hound mongrel.

Feb. 14. Plasma protein level, 6.20 gm.%. Red cell hematocrit, 43%. Bled only twice (total 190 cc.). Started low protein diet (sugar, 118 gm.; lard, 25.5 gm.; butter, 12 gm.; bone ash, 3.1 gm.; salt mixture, 2.1 gm.; cod liver oil, 5 gm.; liver extract, 2.2 gm.; thiamine, 60 I.U.). Weight, 11.2 kg.

Feb. 15 to 26. Ate 100% diet.

Feb. 27 and 28. Ate 75% diet.

Mar. 1 and 2. Ate 50% diet. Weight, 9.8 kg.

Mar. 3 to 17. Supplemented diet with 5 gm. fresh liver daily. Ate 100%.

Mar. 18 to 21. Ate about 50% diet. Increased liver to 10 gm. daily.

Mar. 22 to 25. Ate 100% diet. Plasma protein level (Mar. 23), 4.70 gm.%.

Mar. 26 to 28. Ate only 50% diet.

Mar. 29. Fasted.

Mar. 30. Plasma protein level, 4.60 gm.%. Red cell hematocrit, 30%. *Chloroform anesthesia 15 minutes.* Recovery rapid. Refused food.

Mar. 31. Very sick. Vomited bile-stained mucus several times. Icterus marked. Despite intravenous glucose (40 gm. sugar) and transfusion, dog died. Only slight increase in total urinary nitrogen during 24 hours following anesthesia. Autopsy showed liver lobules standing out uniformly with red central areas and grayish-yellow peripheral areas. Microscopically, the lobules showed about 75% central necrosis. Remaining cells showed extensive fatty degeneration.

EXPERIMENT 5 (Table 1), Dog 38–274, adult female hound mongrel.

Mar. 30. Weight, 9.5 kg. Placed on low protein diet (sugar, 118 gm.; lard, 25.5 gm.; butter, 12 gm.; bone ash, 3.1 gm.; salt mixture, 2.1 gm.; cod liver oil, 5 gm.; fresh pork liver, 5 gm.; thiamine, 60 I.U.).

Apr. 1 to May 15. Average 95% food eaten. Plasma protein level (May 15), 4.50 gm.%. Red cell hematocrit, 47%.

May 16 and 17. Added 23 gm. glycine to regular diet. Ate 60%.
May 18. Added 23 gm. glycine to regular diet. Ate 90%. Weight, 8.4 kg.
May 19. Fasted.
May 20. Gave 23 gm. glycine in water by stomach tube 2 hours before start of *20 minutes of chloroform anesthesia.* (Plasma protein before anesthesia 5.1 gm.%, red cell hematocrit, 47%.) Recovery rapid. Somewhat intoxicated. Refused food.
May 21. Dog found dead in morning. On autopsy grossly liver lobules were uniformly red in central areas, and grayish-yellow in peripheral areas. Microscopically, about 95% of liver lobule showed central hyaline necrosis.

EXPERIMENT 6 (Table 1), Dog 38–81, adult female terrier mongrel.

May 2. This dog was apparently fully recovered from a previous injury produced by 12 minutes of chloroform anesthesia 2 weeks before (described in detail in Exp. 8). Diet same as in Experiment 8 except that vitamins A and D were supplied in the form of navitol. Diet 100% consumed for next 2 weeks. Weight, 6.6 kg.
May 16 and 17. Plasma protein level, 4.08 gm.%. Ate 100% diet.
May 18. Weight, 6.2 kg. Finely powdered xanthine (3.5 gm.) was suspended in 40 cc. normal saline, the mixture boiled for 6 minutes, cooled, and injected subcutaneously on left side. Dog appeared somewhat ill but ate 90% diet.
May 19. Repeated on right side injection of 3.5 gm. xanthine. Dog seems disturbed. Some local heat and tenderness at site of injection of May 18. Fasted.
May 20. Plasma protein level, 3.85 gm.%. Red cell hematocrit, 37%. Fibrinogen, 390 mg.%. *Chloroform anesthesia 20 minutes.* Recovery rapid, but dog clinically ill. Local reaction at site of both xanthine injections. Ate 10% diet offered.
May 21. Very ill. Refused food. Fibrinogen, 89 mg.%. Icterus prominent. Intravenous glucose (sugar 25 gm.). Some vomiting during day.
May 22. Very ill. Refused food. Fibrinogen, 59 mg.%. Icterus prominent. Vomits frequently. Intravenous glucose (50 gm.). Semi-comatose late in day.
May 23. Found dead in morning. On autopsy practically all liver lobules had deep red central areas with yellowish peripheries. Microscopically, there was about 70% central necrosis; intact liver cells showed extensive fatty degeneration.

EXPERIMENT 7 (Table 1), Dog 38–241, adult female hound mongrel.

Apr. 22. Weight, 12.2 kg. Placed on low protein diet (same as diet of Dog 38–274, Exp. 5, Table 1).
Apr. 23 to 29. Fasted.
Apr. 30 to June 2. Ate an average of 95% daily diet. May 15 plasma protein level, 4.85 gm.%; red cell hematocrit, 47%; weight, 11.8 kg.
June 3. Plasma protein level, 4.85 mg.%. Red cell hematocrit, 42%.
June 4 to 11. Ate an average of 50% of daily diet.
June 12. Supplemented daily diet with an additional 15 gm. fresh pork liver daily (total 20 gm. daily).
June 13. Ate 60% diet.
June 14 to 25. Ate an average of 90% daily diet.
June 26. Plasma protein level, 4.70 gm.%. Red cell hematocrit, 54%. Ate 75% diet. Weight, 11.4 kg.
June 27 and 28. Ate an average of 40% diet.
June 29. Replaced daily diet with single feeding of *630 gm. of lean hamburg steak which was promptly consumed.*
June 30. Fasted.

July 1. Plasma protein level had risen to 5.80 gm.%. Fibrinogen, 570 mg.%. Red cell hematocrit, 42%. *Chloroform anesthesia 20 minutes.* Recovery rapid and uneventful. Ate 70% of low protein diet offered.

July 2. Dog in very good condition. No sign of intoxication. Plasma protein level, 5.50 gm.%. Fibrinogen, 550 mg.%. Absolutely no icterus. Ate 95% of low protein diet.

July 3. Fibrinogen, 440 mg.%. Very faint trace of icterus in plasma. Blood formed firm clot readily. Ate 80% diet.

July 4. Fibrinogen, 370 mg.%. Dog in excellent condition. Very faint trace of icterus in plasma. Returned to kennels. Weight, 11.4 kg.

Experiment 7, Table 1, which shows a striking protection against chloroform poisoning due to a single large protein feeding is of such significance that it must be repeated many times. It will be worth while to test the effectiveness of a large injection of plasma protein a few hours before chloroform anesthesia in the protein depleted dog. Experiment 9, Table 3 (Dog 37-177), given below is in complete harmony with Experiment 7, and gives strong support to the observation that protein administration (liver feeding) protects and protein withdrawal in the same dog renders the dog susceptible to chloroform poisoning.

As several of the above experiments (Table 1) showed that 20 minutes of chloroform anesthesia was almost invariably fatal and that even 15 minutes might be fatal, it was decided to try 12 minutes to obtain a severe but non-fatal chloroform injury so that nitrogen partition in the urine might be studied.

TABLE 2.—PROTEIN DEPLETION (PLASMAPHERESIS AND DIET) INCREASES SUSCEPTIBILITY TO CHLOROFORM POISONING AND LIVER INJURY.

Experiment 8—Dog 38-81

Period.		Total nitrogen, mg.	Urea + NH_3 nitrogen.		Uric acid nitrogen, mg.	Fibrinogen,* mg. %.	Icterus index.	Plasma protein level, gm. %.
No.	Length, hrs.		Mg.	%.				
1	48	1410	705	50	11.1			
2	48	1130	670	59	8.0	230	0	4.11
		Chloroform Anesthesia—12 Minutes.						
3	24	1070	790	74	10.7	79	10	4.35
4	24	970	690	72	14.4	116	12	4.42
5	48	1280	810	63	29.7	157	5	3.85
6	48	770	340	45	24.6			
7	48	740	370	49	19.6			
8	48	900	490	55	17.5	210	tr.	4.08
9	48	740	420	56	9.7			

* Fibrinogen and plasma protein figures in this table and Tables 3 and 4 were obtained from blood samples taken at the close of periods indicated.

Table 2 presents data obtained from Dog 38-81, Experiment 8. Following chloroform anesthesia, the rate of urinary nitrogen excretion was nearly double that of the control period, but approached normal within 48 hours in Period 5. The percentage of urea and ammonia nitrogen, which was low in the control periods rose markedly to 74% in the 48 hours after anesthesia, dropped to a low of 45% in Period 6, then rose to control values in Periods 8 and 9. In other

words, the *conservation* of the materials which contribute to the formation of urea and ammonia already conspicuous in the control periods becomes accentuated in Periods 6 and 7.

Figures for *creatine* and *creatinine* are not shown in the table because no significant changes were observed. This is in striking contrast to the large increase in creatine seen in the normal[8] or anemic[1] dog after severe liver injury by chloroform.

The rate of uric acid excretion rose to three times control values in Periods 3 to 5, and returned slowly to normal in Period 9.

The drop in fibrinogen and rise in the icterus index indicate a definite liver injury with central hyaline necrosis.

CLINICAL EXPERIMENTAL HISTORY DURING METABOLISM STUDY PERIOD (Table 2). Dog 38–81, adult female terrier mongrel.

Apr. 7. Plasma protein level, 4.96 gm.%. This dog had been subjected to plasmapheresis for 3½ weeks on a diet similar to that of Dog 37–177 (Exp. 9). Until Apr. 13 ate completely a daily diet of 80 gm. sucrose, 8 gm. filtered butter; 3 gm. salt mixture; 5 gm. cod liver oil; 60 I.U. thiamine; 5 gm. fresh pig liver. Weight, 7.1 kg.

Apr. 13. To remove fats, diet changed to 100 gm. sucrose; 3 gm. salt mixture; 3 gm. bone ash; 40 I.U. thiamine; 7 drops Navitol; 5 gm. fresh liver. Completely eaten on each of following days (Apr. 20 excepted).

Apr. 17. Catheterized and bladder rinsed to start urine collections. Given 200 cc. water daily by stomach tube.

Apr. 20. Dog fasted. Weight, 6.8 kg.

Apr. 21. *Chloroform anesthesia 12 minutes.* Recovery rapid. Ate 100% diet.

Apr. 22. Obviously intoxicated, seems ill. Ate 10% diet.

Apr. 23. Considerably brighter. Ate 90% diet.

Apr. 24 to May 3. Dog in good condition. Weight, 6.5 kg.

Experiment 9, Dog 37-177 (Table 3), differs from those on the other dogs in that the dog was on a *diet containing adequate protein* in the form of 40 gm. of fresh pork liver daily, but the animal's *protein reserves* were kept in a depleted state by the drain of daily plasmapheresis. Twelve days prior to the anesthesia described in this experiment, the dog was given 20 minutes of chloroform anesthesia and showed practically no sign of injury but on no day was the dog deprived of the liver-containing diet. In Experiment 9 the dog was *fasted 24 hours* before, and 48 hours after, chloroform anesthesia, and the blood and urinary findings indicate that at least a moderate liver injury was produced. The absence of the liver diet to compensate for the protein depletion by plasmapheresis here seems to be the factor favoring liver injury. The changes in urinary nitrogen, fibrinogen, and icterus observed here are qualitatively much the same as those seen in Table 2, Dog 38-81. The comparatively high control urea-ammonia nitrogen per cent seen in the preliminary periods is followed by a slight rise in the 48 hours after the chloroform (Periods 3 and 4), and by a significant fall in Periods 5 and 6 ("reaction of conservation") with a return to normal in Periods 7 and 8. The comparatively high control urea-ammonia nitrogen

per cent is to be attributed directly, no doubt, to the higher protein intake. Creatine and creatinine values showed no significant changes and are not here recorded.

TABLE 3.—PROTEIN DEPLETION (PLASMAPHERESIS) INCREASES SUSCEPTIBILITY TO CHLOROFORM POISONING AND LIVER INJURY.

Experiment 9—Dog 37-177

Period.		Total nitrogen, mg.	Urea + NH_3 nitrogen.		Uric acid nitrogen, mg.	Fibrinogen, mg. %.	Icterus index.	Plasma protein level, gm. %.
No.	Length, hrs.		Mg.	%.				
1	48	2200	1660	75.4	11.9			
2	24	1260	950	75.4	4.3	490	0	3.81
			Chloroform Anesthesia—20 Minutes.					
3	24	1330	1030	77.5	6.4	310	14	3.93
4	24	2050	1610	78.5	9.0	56	8	3.75
5	24	1190	830	69.9	16.6	140	9	3.72
6	48	1560	1020	65.7	20.2	264	1 *	4.36
7	48	1920	1460	76.2	25.5	303	1 *	4.44
8	48	2310	1740	75.2	26.8			

CLINICAL EXPERIMENTAL HISTORY DURING METABOLISM STUDY PERIOD (Table 3).

Dog 37-177, female adult poodle terrier mongrel, was depleted by daily plasmapheresis and for 4 weeks before metabolism period, plasma protein level was below 4.6 gm.%. Diet daily consisted of *40 gm. fresh pork liver*, 75 gm. cane sugar, 5 gm. cod liver oil, 13 gm. lard, 5 gm. bone ash, 1 gm. salt mixture.

Dec. 25. Started urine collection. Ate 96% diet. Weight, 6.1 kg.
Dec. 26. Ate 60% diet. Plasma protein level, 4.27 gm.%.
Dec. 27. Fasted.
Dec. 28. *Chloroform anesthesia 20 minutes.* No diet offered. Dog somewhat intoxicated and looks ill, but fairly active.
Dec. 29. Dog obviously ill, although fairly active. Fasted.
Dec. 30. Dog fairly active. Ate 90% diet.
Dec. 31 to Jan. 4. Dog ate average of 90% diet. Very active. Appears normal. Weight, 5.7 kg.

Table 4 summarizes data from Experiments 10 and 11 on the same dog (37-233). Experiment 10 shows the effect of 15 minutes of chloroform and Experiment 11 the effect of 12 minutes of chloroform anesthesia. The results of both experiments are essentially the same and are very similar to those obtained in Experiment 8. In Experiment 10 the total urinary nitrogen excreted in the 48 hours after anesthesia (Periods 3 and 4) was nearly twice that of the control periods, but this is a small absolute increase in total nitrogen. In Periods 5 and 6 the total nitrogen drops toward the initial control values. In the control periods the urea-ammonia nitrogen per cent has the typically low values we have come to associate with the protein-sparing action of a diet high in carbohydrate and fat and very low in protein. The liver injury results in a marked rise of the urea ammonia fraction (Periods 3 and 4) which then falls off to values even lower than those of the control periods. This perhaps

indicates an extremely efficient reaction of conservation on the part of an animal that has comparatively little protein to use for repairing the liver injury plus replacement of general protein wear and tear. The uric acid excretion shows an immediate increase after anesthesia, rising to a maximum in Period 3 and dropping off only very slowly (Exp. 10). Blood fibrinogen falls and the icterus index rises due to the liver injury and the changes are obvious in the 4 days following the chloroform anesthesia. Creatine and creatinine show insignificant changes from day to day and are not included in the table.

TABLE 4.—PROTEIN DEPLETION (BLEEDING AND DIET) INCREASES SUSCEPTIBILITY TO CHLOROFORM POISONING AND LIVER INJURY.

Period. No.	Length, hrs.	Total nitrogen, mg.	Urea + NH_3 nitrogen. Mg.	%.	Uric acid nitrogen, mg.	Fibrinogen, mg. %.	Icterus index.	Plasma protein level, gm. %.
Experiment 10—Dog 37–233								
1	48	1120	625	56	6.9	..	0	
2	48	1050	595	57	6.4	386	0	5.18
Chloroform Anesthesia—15 Minutes.								
3	24	1020	722	71	9.2	292	17	5.00
4	24	1050	748	71	10.4	194	15	4.99
5	24	796	506	64	12.2	135	15	4.65
6	24	592	309	52	10.1			
7	48	940	445	47	20.8	253	1+	5.22
8	48	891	392	44	18.0			
9	48	842	418	50	18.0			
Experiment 11—Dog 37–233								
1	48	846	464	55	6.2	346	0	5.15
Chloroform Anesthesia—12 Minutes.								
2	24	1030	786	76	22.4	166	17	4.60
3	24	983	703	72	35.5	78	16	4.82
4	48	1080	618	57	61.7	131*	15*	4.60*
5	48	885	413	46	60.1			
6	48	832	381	46	62.2	195	1+	

* Average of figures for two 24-hour samples.

CLINICAL EXPERIMENTAL HISTORY DURING EXPERIMENTS 10 AND 11.

EXPERIMENT 10, Dog 37–233, Boston bull female.

Dec. 28. Plasma protein level, 6.41 gm. %. Red cell hematocrit, 53%. Started bleeding and low protein diet (sugar, 118 gm.; lard, 25.5 gm.; butter, 12 gm.; bone ash, 3.1 gm.; salt mixture, 2.1 gm.; liver extract, 2.2 gm.; thiamine, 60 I.U.). Weight, 11.6 kg. Bleeding at intervals continued to Feb. 4. Ate average of 65% diet in this period.

Jan. 30. Gave 64 mg. colloidal iron* by vein because of low hematocrit.

Feb. 11. Gave another 64 mg. colloidal iron by vein.

Feb. 23. Supplemented diet with 5 gm. liver daily.

Feb. 25. Started urine collection and metabolism study. Ate 50% diet.

Feb. 26. Ate 50% diet.

Feb. 27 and 28. Fasted.

Mar. 1. Weight, 9.1 kg. *Chloroform anesthesia 15 minutes.* Recovery rapid. Ate 80% diet offered.

* We are indebted to Dr. David Loeser of Loeser Laboratory Inc. for a supply of this material.

Mar. 2. Somewhat ill. Refused food.
Mar. 3. More active but refused food.
Mar. 4. Ate 10% diet.
Mar. 5. Ate 100% diet.
Mar. 6 and 7. Ate average of 50% diet.
Mar. 8 to 11. Ate average of 60% diet. Weight, 8.7 kg. Dog in good condition at end of experiment.

EXPERIMENT 11, Dog 37–233.

Mar. 15. Weight, 9.7 kg. Diet changed by removing liver extract and adding 20 gm. fresh pork liver daily. Ate 90% diet.
Mar. 16 to 31. Ate average 60% diet.
Apr. 1. Started urine collection and metabolism study.
Apr. 2. Fasted.
Apr. 3. *Chloroform anesthesia 12 minutes.* Recovery rapid. Ate 40% diet.
Apr. 4 and 5. Somewhat intoxicated and ill. Ate average 55% diet.
Apr. 6. Ate 15% diet.
Apr. 7 to 13. Ate average 50% diet. Dog returned to kennel in good condition, weighing 7.8 kg.

Discussion. The following paper by Messinger and Hawkins gives experimental data indicating the importance of diet during administration of arsenicals and their experiments are in harmony with the chloroform experiments recorded above. Practically all workers in this field agree that sugar and proteins have some protective action, that fat gives no protection and may actually predispose to liver injury. The older literature and theories were reviewed some years ago by Davis and Whipple.[3] Recent experiments by Goldschmidt, Vars and Ravdin[6] show that mice are protected by protein diets against chloroform anesthesia. They state[12] that sodium ricinoleate and xanthine protect against chloroform poisoning and believe the reaction to be non-specific.

It is well to admit first as last that we do not have any satisfactory hypothesis to explain the toxic action of chloroform upon liver cells. Of all the many proposals none gives the slightest comfort to those who would understand why the liver cells are picked out in preference to other active cells rich in ferments, for example, pancreas and kidney. Some authors[7,10] ascribe the chloroform injury to phosgene or hydrochloric acid liberated by the cellular oxidation of chloroform. Davis[2] has reported experiments which rather effectively dispose of the thesis that chloroform liver injury is due to disturbance of cell oxidation. The failure of large glycine feedings to prevent serious liver injury from 20 minutes chloroform anesthesia (Exp. 5, Table 1) may be used in the argument that the deamination of glycine in the liver (with ammonia liberated) does not protect against chloroform liver injury as explained on the theory of free hydrochloric acid derived from the chloroform by cellular oxidation. Whatever explanation is preferred, glycine does not protect.

There is pretty general agreement that carbohydrate does give some protection against chloroform liver injury.[4] In view of the great importance of the cell protein stores, it may be argued that

the efficacy of the carbohydrate diet is due to "protein-sparing at the source" and therefore is not primary but secondary.

Clinically and anatomically the *protein depleted* dog shows signs of severe liver injury (Exps. 8, 9, 10, 11) but the increase in total urinary nitrogen is small compared with that recorded for the *non-depleted* dog with a severe liver injury.[1,4] We may choose to explain this observation as due to a diminished store of body protein vulnerable to insult by toxic split products derived from the dead and autolyzing liver cells, or to a very efficient reaction of nitrogen conservation, or both. The very low figures for percentage of urea and ammonia in the urine indicate that the conservation of nitrogenous material becomes accentuated when the liver injury is being repaired.

No significant changes in creatine excretion following liver injury in the protein depleted dog are recorded. This is in conspicuous contrast to the large increases in creatine excretion observed in the normal or anemic non-depleted dog due to chloroform liver injury.[1] Assuming that practically all creatine is found in the muscles we may relate this difference to the presence of protein stores in the muscles which are injured and as a result creatine is set free. The alternative is to us less probable—that all creatine set free is recaptured or used in the emergency due to protein depletion and protein deficiency.

The large increase in uric acid excretion following chloroform in the depleted dog is comparable to that seen in the normal dog;[14] this along with the pronounced fall in blood fibrinogen is evidence that the liver injury produced by the short period of anesthesia in the depleted dog is fully as severe as that produced by the longer period of anesthesia in the normal dog. The fact that the enhanced uric acid excretion continues over a much longer period in the depleted dog than in the normal dog is perhaps referable to the slower repair of injured liver tissue in the former.

Summary. Liver injury due to chloroform anesthesia increases in extent as the protein body stores are depleted. In a protein-depleted dog 15 to 20 minutes of chloroform anesthesia is frequently fatal with extensive hyaline liver necrosis and the typical picture of chloroform poisoning. Twelve minutes of chloroform anesthesia in a protein-depleted dog will cause moderately severe liver injury. Protein depletion is effected by low protein diets alone or combined with bleeding or plasmapheresis.

Control experiments in dogs without protein depletion indicate that 90 minutes of chloroform anesthesia can be tolerated with but little liver injury.

In the depleted dog xanthine subcutaneously or glycine by mouth do not protect, but a single large protein feeding 36 hours before chloroform anesthesia may protect against liver injury.

In contrast to the non-depleted or anemic dog the urinary creatine does not increase after liver injury in these protein-depleted dogs.

The protein-depleted dog compared with the non-depleted dog after chloroform liver injury shows relatively little increase in total urinary nitrogen.

There is a conspicuous increase in uric acid excretion in these depleted dogs after chloroform liver injury, perhaps due in part to liver function impairment and disturbance of its normal capacity to convert uric acid to allantoin.

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ARSPHENAMINE LIVER INJURY MODIFIED BY DIET. PROTEIN AND CARBOHYDRATE PROTECTIVE, BUT FAT INJURIOUS.

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Since the arsenical compounds have proved so effective in the antisyphilitic treatment, countless numbers of patients receive such drugs for extended periods. One of the not too uncommon complications arising from the use of arsenicals is injury of the liver of varying degrees of severity. The problem as to how to prevent and treat such injuries continuously confronts the clinician. Since Davis and Whipple[2] demonstrated that carbohydrates protected the liver against chloroform injury and also aided in its regeneration, it has been customary practice to administer carbohydrates in liberal amounts in any type of liver injury.

In 1931 Craven[1] reported that he found a high fat diet most efficacious in preventing "acute yellow atrophy" of the liver of dogs, due to arsphenamine. Both protein and carbohydrate diets were reported as inferior. He based his findings on the histologic changes present in the livers. Schifrin[4] stated that contrary to Craven's report he found a protein diet was more satisfactory than

fat in minimizing arsphenamine injury and that from histologic study regeneration was more rapid and complete with the meat diet.

Obviously the question of arsphenamine liver injury which is of acute interest to the clinician is open for discussion, with conflicting claims coming from relatively similar experiments.

In our experiments we have used comparable types of diet and the evidence is clear-cut that the meat diet is very effective in protecting the liver against arsphenamine injury. Carbohydrate is of distinct protective value. Fat diets are deleterious, as the injury that follows the injection of arsphenamine may be severe and progressive with death resulting from liver insufficiency.

In confirmation of the value of protein as a protective agent against liver injury are the data reported by Miller and Whipple in an accompanying paper. They have demonstrated that when the protein stores of a dog are depleted that the liver becomes very sensitive to chloroform and that extensive injury results from only 15 to 20 minutes of light chloroform anesthesia.

Methods. The dogs used were all healthy young mongrel adults weighing from 10 to 17 kg. In each experiment there was as a rule 1 dog on each type of diet and the arsphenamine was given according to weight. The initial dose was 0.03 gm. per kg., with increase from week to week as indicated in the tables. A standard brand of arsphenamine was used and the same lot of drug was given throughout an experiment so that any possible variations in toxicity of different samples are ruled out. The drug was injected by means of a gravity burette into the external jugular veins.

The carbohydrate diet consisted of steamed rice, cane sugar, 20 gm.; dextrose, 15 gm.; Wesson salts, 4 gm.; cod-liver oil, 5 cc.; thiamine chloride, 33 units; Klim, 10 gm. (a whole milk powder), with water added to make it into a semifluid mass. From 600 to 800 gm. of this mixture was fed daily and the dogs maintained their weight. By macro-Kjeldahl analysis this diet contained an average maximum protein value of 3.5%.

The fat diet was composed of lard, 70 gm.; protein-free butter fat, 50 gm.; cod-liver oil, 50 cc.; kaolin, 2 gm.; bone ash, 4 gm.; Wesson salts,[5] 4 gm.; and thiamine chloride, 33 units. The dogs ate the diet satisfactorily and were maintained in good clinical condition.

The protein diet consisted of 1 pound of hamburg with low-fat content.

The icteric index was estimated directly on plasma obtained from centrifugalized oxalated blood samples in hematocrit tubes, comparing with color standards according to the method of Farahaugh and Medes.[3]

Experimental Observations. Since all the experiments were carried out under standard conditions we have listed the dogs in tables according to the diet fed, rather than discussing each of the experiments separately. Such grouping of the dogs allows for more brevity and also for more clarity of exposition and brings out contrasts between the three groups.

All of the dogs (Table 1) except 38–169 were fed their protein diet for 1 week before the initial injection of arsphenamine. Dog. 38–169 for a month preceding the meat diet received kennel diet plus ½ pound of salmon so as to be certain its protein stores would be replete. Under the heading icteric index the "0" day represents

the day of injection and the control level of the icteric index found in the sample of blood withdrawn just prior to the injection of the drug.

TABLE 1.—PROTEIN DIET.

Dog.	Arsphenamine, gm./kilo.	Icteric index. Days after injection. 0	1	2	3	4	5	6	7	Biopsy liver injury.
38–53	0.030	0	2	1						
	0.035	0	5	3						
	0.040	2	3	2						Slight
38–169	0.035	0	–	0	0					
	0.040	0	0	1	0					
	0.045	0	0	0						
38–19	0.040	0	2	1	1	0				
	0.045	0	0	0						
38–94	0.035	0	3	2						
	0.040	0	0	1						
	0.045	0	1	0	0					Slight
38–62	0.030	0	1	0						
	0.035	0	0	–	0	0				
	0.040	0	–	0	0					
	0.045	–	1	1						
	0.050	1	–	2	2	–	1			Slight

Arsphenamine injected at weekly intervals.

It is apparent that the high-protein diet was most effective in protecting the liver against severe injury, as at no time was there any conspicuous elevation of the icteric index. Histologic examination of the livers showed minimal injury. The dogs continued to eat their full ration and never showed the slightest evidence of clinical intoxication.

Dog 38–53 was killed with ether on the third day after the last injection and autopsied together with the dog on the high-fat diet which became very ill following the third injection of the drug. At autopsy no gross abnormalities were found in Dog 38–53. Histologic sections of the liver showed that cells in the central area had been injured and the cell débris cleared away leaving collapsed stroma. Occasional portal areas showed similar loss of cells but the lesion was mainly central. There were some phagocytic cells containing brown pigment which was apparently lipochrome in character. Special stains revealed no fat and some glycogen was found in liver cells.

Biopsy of the liver of Dog 38–94 showed a minimum amount of injury with loss of a few cells in the central areas. Biopsy was done on the sixth day after the last injection of the drug. In portal areas there were occasionally a few necrotic liver cells surrounded by neutrophils. Some glycogen was present in the liver cells but no fat. Pigmented phagocytic cells were to be seen in the areas that had been injured.

Biopsy from Dog 38–62 on the third day after the last injection showed a similar picture as regards extent of damage. Occasional mitotic figures were present indicating regeneration.

TABLE 2.—CARBOHYDRATE DIET.

Dog.	Arsphenamine, gm./kilo.	Icteric index. Days after injection. 0	1	2	3	4	5	6	7	Autopsy liver injury.
38–189	0.040	0	0	0	1	0				
	0.045	0	1	0						
	0.050	0	1	2						
38–179	0.035	0	–	0	0					
	0.040	–	2	0	0					
	0.045	–	0	0						
38–50	0.030	0	0	0	–	0				
	0.035	0	–	4	1					
	0.040	1	3	2						Slight
38–96	0.035	0	24	38						Lethal
38–63	0.030	0	0	–	0	0				
	0.040	0	–	2	1					
	0.045	1	–	2	1					
	0.050	3	3	7	9					Slight
38–143	0.030	0	8	3	–	5				
	0.035	4	6	–	19	21	12	–	12	
	0.040	0	–	4	4					
	0.045	4	–	7	6					
	0.050	5	–	12	–	15				Moderate

The dogs received the carbohydrate diet for a week previous to the first injection of the drug. Dog 38–179 was fed ½ pound of salmon on the kennel diet for a month prior to the carbohydrate feeding, so its stores of protein must have been adequate. If we momentarily disregard Dog 38–96 and Dog 38–143, it then appears that on comparable regimens these carbohydrate dogs have an icteric index picture closely simulating that of the protein dogs. The histologic sections, however, reveal that there was a little more injury to the liver and the dogs did show slight intoxication following the injection of the drug, as they left some food for a day or two. Recovery was prompt, however.

Dog 38–96 was apparently very susceptible to the arsphenamine, as the initial dose of 0.035 gm. per kg. caused severe reaction. It showed diarrhea, bouts of vomiting, and on the morning of the third day was found dead. Autopsy revealed generalized jaundice, and petechial hemorrhages were present in the subcutaneous tissues. The liver grossly was light brown in color with numerous pin-point red and yellow areas on the surface. The cut surface was friable, and central areas were red in color and tended to be sunken below the surface. Sections showed extensive hyaline necrosis with neutrophil infiltration with only a few liver cells remaining about the

portal areas and some of them contained fat. No glycogen was found in the persisting liver cells.

Dogs 38–50, 38–63, and 38–143 were killed with ether on the second or fourth day after the last injection and autopsied at the same time as comparable dogs on the fat diet. Grossly, the organs presented a normal appearance.

The sections of liver from Dog 38–50 again showed only slight injury in the central areas with loss of a few liver cells. No areas of hyaline necrosis were found. Pigmented phagocytic cells were present in the injured areas. The liver cells contained a large amount of glycogen and no fat was present. The liver of Dog 38–63 was similar in appearance.

Dog 38–143 showed more injury, as these areas about central and portal areas were larger. No hyaline necrosis was found, but there was loss of liver cells with numerous pigmented phagocytic cells. There was only a moderate amount of glycogen in the liver cells and no fatty degeneration was apparent.

It is apparent that carbohydrate afforded protection but not quite as much as the meat diet.

TABLE 3.—FAT DIET.

Dog.	Arsphenamine, gm. /kilo.	Icteric index. Days after injection. 0	1	2	3	4	5	6	7	Autopsy liver injury.
38–211	0.035	2	–	4	2					
	0.040	2	15	16	35	48				
38–54‡	0.030	0	0	0						
	0.035	0	6	2						
	0.040	2	24	51						Slight
38–158*	0.040	0	4	3	2	0				
	0.045	0	19	79	159					Moderate
38–52†	0.035	0	–	–	46	52	45			
	0.040	39	–							Lethal
38–48	0.030	0	9	4	6					
	0.035	4	6	6	8	13	7			
	0.040	6	8	6						
	0.045	5	13	13	7	–	–			
	0.050	18	–	83						Moderate
38–67	0.035	0	6	4	3	2				
	0.040	2	4	4	4					
	0.045	0	10	15	21	35	36			Severe
38–62	0.035	0	–	8	18	11	9			
	0.040	7	10	13	19	10	9			
	0.045	7	–	23						Moderate

* 10% protein added to fat diet. † 20% protein added to fat diet.
‡ 30% protein added to fat diet.

In Table 3 the data obtained from the high-fat diet dogs are tabulated. Dog 38–211 received kennel diet and ½ pound of salmon for a month prior to receiving the fat diet. All of these dogs showed a drop in total plasma proteins after being on the fat diet from 7 to

10 days. This change was, on the average, a fall from a normal value of 6.4% to a lower value of about 5.5%. The carbohydrate dogs did not show any decrease in their plasma protein levels. This decrease in plasma protein, although slight, may be an indication that protein stores were being drawn upon, since the fat diet would scarcely protect the protein stores as carbohydrate may do.

All of the fat-fed dogs were easily injured by the arsphenamine, as indicated by the icterus that developed. On continued administration of the drug, progressive jaundice developed and intoxication was so marked that death occurred; or they were killed with ether, because it was obvious that death would ensue. The addition of varying amounts of protein to the fat diet of 3 of the dogs had no significant mitigating effect on the toxic reaction.

Dog 38–52 was found dead on the morning after the second injection. Its initial response to the first dose of the drug was severe, as seen in the table, and we were not surprised at the early fatal outcome. The other dogs were killed with ether, except Dog 38–211 which will be discussed under Table 4.

At autopsy, all the fat-fed dogs showed generalized jaundice and some exhibited bleeding tendencies due to lack of fibrinogen, prothrombin, or both. The livers were a light brown-yellow in color and obviously fatty. They tended to be friable and the central portions of the lobules frequently were depressed slightly below the surface. The dogs were killed and autopsied on the second, third, or fifth days after the last injection of arsphenamine.

Dog 38–52 showed very extensive liver injury as at least one-half of each lobule had been destroyed. All liver cells about the central areas were gone and there was hemorrhage and wandering-cell infiltration with considerable brown pigment in the large phagocytic cells. On the periphery there was fatty degeneration, and it was only about portal areas that one found relatively normal-appearing liver cells. With special stains even these latter cells were found to contain fat. No glycogen was present.

Dog 38–54 showed generalized fatty degeneration, but only occasional necrotic liver cells. Bile canaliculi contained brown inspissated bile. No glycogen remained.

Dog 38–48 showed a moderate degree of fatty degeneration with a little glycogen persisting. There was collapse of central areas with loss of liver cells. Some mitotic figures were present and there were many pigmented phagocytic cells. Areas of injury were found about portal regions also.

Dog 36–159 showed marked fatty degeneration with areas where liver cells had been destroyed and one saw only stroma and phagocytic cells. Both central and portal regions were involved. There was some glycogen in better preserved liver cells. Kidney tubules contained bile-stained material and some of the epithelium of collecting tubules contained fat.

Dog 38–67 showed hyaline necrosis of approximately one-quarter

of each lobule and in addition there was evidence of previous loss of cells. Phagocytic cells containing brown pigment were present. The lesion was both central and portal in distribution. Fat was present in many of the remaining liver cells and no glycogen was found.

TABLE 4.—THE EFFECT OF INTERCHANGING DIETS.

Dog.	Diet.	Arsphenamine, gm./kilo.	Icteric index. Days after injection.								
			0	1	2	3	4	5	6	7	8
38–211 . . .	Protein	None	48	–	24						
		0.045	21	20	13	–	–	–	10		
		0.040	5	4	4	3					
		0.045	2	2	2	2	2				
	Fat	None	2	–	–	–	21				
		0.050	21	–	26	–	–				
38–169 . . .	Fat	0.040	0	5	4	4					
		0.045	3	21	28	34	37				
	Protein	None	37	21	–	–	–	–			
		0.050	6	6	5	–	4				
	Fat	None	3	–	5	–	–	27	26	–	11
38–189 . . .	Fat + 20% protein	0.050	0	12	25	–	77				
	Carbohydrate	None	77	63	–	14					
	Fat + 20% protein	None	14	14	12	8					
		0.050	7	–	48	55					
38–179 . . .	Fat	0.040	2	12	10	6					
		0.045	2	4	4	3	2				
		0.050	7	17	33	16					
38–19 . . .	Fat	None	0	–	–	–	4				
		0.050	4	16	16						
	Carbohydrate	None	16	–	–	–	–	–			
		0.050	2	–	4	2					
		0.050	1	–	2	1					

Dog 38–62 previously had been fed protein and a biopsy taken after 5 injections of the arsphenamine showed only minimal injury as described. After it had been on a fat diet and had received 3 doses of arsphenamine, the liver sections showed extensive injury with loss of liver cells in portal or central areas. There was some fatty degeneration, and some necrotic liver cells were to be seen. There were mitotic figures indicating attempted repair. No glycogen was present.

Review of these sections indicates different types and different grades of injury and it is impossible to predict from histologic changes what the icteric index might be or how severe was the state of intoxication.

In Table 4 we have listed a group of animals who have previously appeared in the other tables according to the diet fed them. When Dog 38–211 on the high-fat diet became toxic and inactive with an icteric index of 48, as seen in Table 3, we substituted the protein diet for the high-fat diet in an effort to save this animal. Promptly the icterus level began to fall and the dog became active again.

Despite 3 subsequent arsphenamine injections, the bilirubinemia continued to decrease and the dog appeared well. Once again, as seen in Table 4, the dog was returned to its original high-fat diet, and after 4 days the icteric index had risen from 2 to 21 units simply on change from protein to fat diet without further arsphenamine. We shall again refer to this phenomenon of apparent "delayed jaundice."

Further evidence that Dogs 38–169 and 38–179 were really protected by their respective protein and carbohydrate diets and not refractory to arsphenamine appears when both were placed on fat diets for 1 week and then injected again as indicated in Table 4. Dog 38–169 in particular showed the typical progressive jaundice on the high-fat diet and at the maximum time of injury it had an icteric index of 37, was listless and toxic. We again resorted to the protein diet to save this animal. The icterus soon began to clear and despite another injection of arsphenamine the icterus continued to recede, as the table shows, and the animal remained in such excellent condition that it could be used in the following experiment.

In an effort to reproduce the "delayed jaundice" observed in Dog 38–211, the protein diet of Dog 38–169 was now withdrawn and replaced again by the high-fat diet. As indicated in Table 4, without any further administration of arsphenamine, the dog's plasma bilirubin showed a sharp increase from 3 to 27 units by the fifth day. On the sixth day the icteric index was still 26 and then gradually returned to normal.

The results of feeding the fat diet to protein Dog 38–19 are indicated in Table 4 by the slight but definite "delayed jaundice." The further injurious effect on this dog of another injection of arsphenamine is apparent. Upon again changing this dog's diet from fat to carbohydrate, we see a diminution of the icterus and lack of injurious response despite further arsphenamine administration.

Carbohydrate Dog 38–189 was placed on a fat diet plus 20% protein since little injurious response was obtained on its original carbohydrate diet. After eating the fat diet for a week it was injected as shown in Table 4 and developed the usual severe toxicity and bilirubinemia the dogs on these diets show. The beneficial effect of replacing the fat diet by carbohydrate is further demonstrated. An attempt to reproduce "delayed jaundice" by reversion to the fat diet failed here, but the prompt injurious response of the animal on the fat diet again to arsphenamine was demonstrated, despite the added protein in the fat diet.

Discussion. It is of importance to appreciate the fact that even the initial dose of arsphenamine given to these dogs is large. When one considers that an 11-kg. dog receives a minimum of 0.33 gm. of the drug in a single dose, as compared to 0.4 gm. therapeutic dose for a 66-kg. man, it is to be expected that the liver should be injured regardless of the diet fed. Sections of the livers of all the dogs show that some injury has occurred. In the case of the protein-

fed dogs, it is minimal and the liver derangement is so slight that the function of eliminating bile pigments has not been particularly disturbed. In the carbohydrate group the degree of injury as indicated by the icteric index and the histologic changes in the liver varies, but it compares in no way with the extensive damage and dysfunction as exhibited by the fat-fed dogs.

One should note well the fact that dogs that had been protected by meat or carbohydrate diets, when changed over to the fat diet, sustained severe liver injury upon subsequent injection of arsphenamine. This demonstrates that these dogs were not refractory to the drug and also indicates that high-fat diet is injurious, even though the animals' stores of protein may be high.

Conversely, when the fat-fed dogs were severely jaundiced and intoxicated and would not eat well, there was immediate improvement in their condition when the diet was changed to protein or carbohydrate. No further injury occurred to their livers when arsphenamine was subsequently injected.

Further evidence that fat is deleterious is indicated by the data in Table 4. Some of the dogs showed a decided increase in their icteric index when their diets were changed to fat, even though no more arsphenamine was given during the period of fat diet. It is possible that this "delayed jaundice" is caused by fat deposited in the liver which renders the cells susceptible to some arsenic that was present in the body from previous injection. It is not just a flight of fancy to consider that delayed liver injury as displayed by some human beings may be related to their dietary régime.

A high-fat diet may be injurious due to its requirements of sugar for its combustion. This would imply a drain first on the carbohydrate stores and finally on the protein stores. The total plasma protein of the fat-fed dogs showed a slight decrease after 7 to 10 days' feeding and this may be of significance, indicating that the dogs were calling upon their protein stores.

We believe Craven's conclusions are in error mainly because he killed his animals at the first sign of serum jaundice. Deductions drawn from the histopathologic changes in the livers of dogs killed at this stage of the injury could readily lead one to error. It is necessary to follow the animals over considerable periods to observe the icteric index and general clinical developments.

Schifrin[4] disagreed with Craven's conclusions, as he found the protein-fed dogs showed the least injury and that the liver regenerated best on the meat diet.

The value of protein as a protective agent appears to be clearly established, but further studies are required to learn the why of its beneficial effects. It has been customary to give liberal amounts of carbohydrate to patients with liver injury. Some clinicians consider that protein should be restricted in order not to tax the damaged liver. In our experiments, the dogs with severe liver injury showed marked improvement when the fat diet was changed to

protein and there was not the slightest evidence that the meat diet was in any way injurious. We suggest that in the face of liver injury a diet of protein and carbohydrate may prove to be of more value than carbohydrate alone.

Summary. When dogs are given arsphenamine in doses of 0.03 gm. per kg. or higher, liver injury results to a greater or lesser degree depending on the diet fed. Protein is found to be most effective in protecting dogs against arsphenamine liver injury. On a protein diet the liver injury is trivial and promptly repaired. A carbohydrate diet also is beneficial, but is not as uniformly protective and the liver injury may be somewhat greater. Fat has proved to be deleterious, as the arsphenamine dogs show marked progressive jaundice, severe liver injury, and may become intoxicated to the point of death.

In certain instances dogs that had been protected by protein or carbohydrate showed a progressive increase in the icteric index when changed over to the fat diet, even though no additional arsphenamine was injected.

When fat-fed dogs that showed severe intoxication due to arsphenamine injury were switched to protein or carbohydrate diets they immediately recovered from the intoxicated state and the icteric index decreased. Subsequent injections of arsphenamine caused no ill-effects as long as the dogs remained on either the protein or carbohydrate diet.

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USE OF VAPORIZED BRONCHODILATOR SOLUTIONS IN ASTHMA AND EMPHYSEMA.

A Continuous Inhalation Method for Severe Asthmatic States.

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Inhalation of vaporized solutions of bronchodilator drugs by patients with asthma or emphysema has been used for many years. In simplicity of technique, rapidity of action, and in relative freedom

from constitutional side-effects, this method offers practical advantages over the administration of similar drugs by mouth or by hypodermic injection. The extent of distribution and absorption of such solutions, administered by methods of continuous or intermittent inhalation, was studied some years ago by Heubner.[6] Lageder[7] observed increase in vital capacity and velocity of breathing, as well as beneficial clinical results, following continuous inhalation of 1:1000 epinephrin vaporized over 20-minute periods.

The most important advance in practical therapy was made by Graeser and Rowe[4] in 1935, with the introduction of a more concentrated (1:100) solution of epinephrin, used in a hand-bulb atomizer that provided a fine vapor suitable for inhalation. Oral inhalation of vaporized 1:100 epinephrin solution has since been widely used for relief and prevention of asthmatic attacks.

In his most recent paper, Graeser[3] has presented an excellent brief review of earlier work, together with some further observations on the use, by the hand-bulb atomizer, of solutions of epinephrin of various concentrations, and of certain other solutions, notably ephedrin sulphate 10%, and neosynephrin 5%. Graeser concluded that epinephrin 1:100 was, under average conditions, the most practical for the inhalation therapy of bronchial asthma. In some instances, a 1:50 concentration was found to be more effective; in others, 1:200, or lower, was adequate. Inhalation of 10% ephedrine, or of 5% neosynephrin solution, did not give relief. In some instances with children, the use of a mask apparatus, with a motor blower providing a continuous vaporization, was necessary.

It is generally recognized that the hand vaporizer with 1:100 epinephrin solution, has both limitations and disadvantages: 1, It is usually employed for only a few seconds at a time, and the application of the vapor to the bronchial mucous membranes is therefore brief; often insufficient in more severe asthmatic attacks; 2, even the squeezing of the nebulizer and the repeated deep inhalations may be exhausting to a very ill or dyspneic patient; 3, epinephrin 1:100 on prolonged use may be drying and irritating to mucous membranes (Galgiani, Proescher, Dock, and Tainter[2]); 4, this solution, if used intensively or repeatedly over long periods, will in some cases produce undesirable systemic effects, such as headache, palpitation, nervousness, tremor, and so on.

In an attempt to overcome some of these difficulties, we have employed a simple technique for *continuous inhalation* of vaporized bronchodilator solutions. This consists in the use of a pressure tank of oxygen, with the usual reducing valve to regulate flow; attaching the outflow tube to the vaporizer and running in oxygen, at a flow sufficient to produce adequate vaporization. A small motor blower unit can be used instead of a pressure tank; but in our experience, these units usually convey a slight odor to the vapor, which is often disagreeable to the patient.

With a flow of 4 to 7 liters per minute, 1 cc. of solution will be vaporized in from 3 to 10 minutes. The patient simply holds the nozzle of the vaporizer in his oro-pharynx, and breathes quietly; no additional effort is needed.

Two advantages are obtained by this technique: 1, A larger amount of solution is brought into contact with the bronchial mucous membrane than is possible with the use of the hand-bulb, and without effort on the part of the patient. The technique is thus more effective for the very ill bed patient in a severe asthmatic state. 2, Less irritating solutions, with milder bronchodilator action, are often effective in suppressing moderate asthmatic attacks when given by the continuous technique, whereas they are ineffective when used with the hand spray. This is of particular advantage in patients who suffer from dryness and irritation of the air passages after inhalation of vaporized 1:100 epinephrin solution, or when constitutional side-effects occur; especially if such patients have to use the spray frequently during the day, and over prolonged periods of weeks or months.

Neosynephrin hydrochloride is a mild bronchodilator of this type. This substance is chemically closely similar to epinephrin hydrochloride, differing only in having one, instead of two, hydroxyl radicals attached to the benzene ring. It is established as effective in constricting nasal mucous membranes by topical application.[1,5,11] Neosynephrin is said (Fitzhugh[1]) to induce a more lasting vasoconstriction than either ephedrin or epinephrin, when applied locally. After-effects of dryness, irritation, and engorgement apparently do not occur. By subcutaneous injection, this drug has little effect in relieving asthma.

Procedure. The technique of continuous vaporization of bronchodilator solutions has been used at the Presbyterian Hospital during the last 18 months, for the treatment of bronchial asthma, and for asthmatic attacks, dyspnea, and cough in patients with pulmonary fibrosis, chronic emphysema and certain cases of bronchopneumonia. Though administered for the most part to bed patients, it has also been tried in ambulatory patients in the Asthma Clinic and the Chronic Chest Disease Clinic.

As stated above, a single treatment consisted in the vaporization, over 3 to 10 minutes' time, of 1 or 2 cc. of bronchodilator solution, the subject holding the nozzle well within his oro-pharynx and breathing quietly throughout the procedure.

As a vaporizer we used the "Vapco" and the "Vaponefrin" models. Both were satisfactory; the Vaponefrin apparatus produced a somewhat more voluminous vapor stream.

Solutions.* In addition to 1 to 100 epinephrin solution, and 1 to 100 neosynephrin solution, we tried mixtures of epinephrin and neosynephrin, and "Vaponefrin" solution, a proprietary product whose composition is stated by the manufacturer to "contain 1 to 100 epinephrin, and 0.5 per cent chlorbutanol."

* The neosynephrin solution used in this study was supplied through the courtesy of Frederick Stearns & Co.; the Vaponefrin vaporizers and solution through the courtesy of the Vaponefrin Company.

Results. In addition to clinical results observed, an attempt was made to obtain an objective measure of change in pulmonary function, in patients who were not seriously ill and who could coöperate in performing respiratory tests. Pulmonary ventilation, vital capacity, and maximum ventilatory capacity were measured in a number of such patients.

There were no consistent changes in resting pulmonary ventilation.

Considerable and significant increase in vital capacity was noted, following continuous inhalation of the spray, in most of the cases of chronic fibrosis and emphysema, and in a number of asthmatic subjects. The results in 26 unselected cases are given in Table 1. This series consisted in 12 ambulatory cases of asthma, studied in the Asthma Clinic, 3 ambulatory cases of chronic emphysema and 9 hospitalized cases of chronic pulmonary disease of various types.

In general, the degree of relief obtained was approximately proportional to the increase in vital capacity.

The ambulatory asthmatic subjects coming in to the Clinic were given the inhalation whether they were having asthmatic symptoms at the time, or not. This probably accounts in part for a large discrepancy in vital capacity change, in individual cases.

In a few instances we have had patients in status asthmaticus who have responded to continuous inhalation spray when other measures have failed. These patients were usually too ill for any respiratory measurements.

Such a case was N. R., a Post Office clerk of 33, who had had bronchial asthma for 4 years. For 2 days prior to his hospital admission, he had been in an almost continuous asthmatic state. This attack had not responded to epinephrin given hypodermically every 2 hours, nor to ephedrin by mouth, about 15 tablets a day. After admission to the hospital, a further injection of epinephrin, and 1 of morphine and atropine, gave no relief. Dyspnea and cough were severe. Half an hour later an inhalation spray, consisting of 7 drops of epinephrin 1 to 100 and 10 of neosynephrin 1%, was given continuously over a 15-minute period. The change in the patient's condition following the inhalation spray was immediate and striking. Pulse dropped from 130 to 100, respirations from 60 to 40, inspiratory stridor disappeared and expiratory stridor was much decreased. Subjectively, dyspnea was relieved. During that night the spray was used 4 times, bringing marked relief on each occasion. No other medication was used except for nasal oxygen, and amytal tablets. During the ensuing 3 days, the spray was used at frequent intervals, for recurring severe asthma. He was much improved. On the fourth day, he was found to respond again to epinephrin hypodermically. Subsequently, the maxillary sinuses were drained, and the asthma gradually subsided.

The subjects with chronic pulmonary disease were having more continuous symptoms, of dyspnea, asthma and cough, than the ambulatory asthmatic cases, and, as would be expected, their responses to the continuous spray were more uniform.

TABLE 1.—VITAL CAPACITY BEFORE AND AFTER CONTINUOUS INHALATION SPRAY.

Disease.	No. of cases.	Type of treatment.*	Total number of treatments given.	Average vital capacity, cc.		
				Before.	After.	% change.
1. Bronchial asthma	14	Epinephrin	10	2230	2485	+11.5
		Neosynephrin	18	2090	2340	+11.9
		Vaponefrin	4	1635	2045	+25.1
		Neo.-epi.	2	2350	2410	+2.6
2. Chronic emphysema	9	Epinephrin	7	1745	1905	+9.2
		Neosynephrin	19	1880	2080	+10.6
		Vaponefrin	2	1525	2000	+31.0
		Neo.-epi.	6	1495	1660	+11.0
		Neo.-vapo.	3	1585	1835	+15.8
3. Tuberculosis and pulmonary fibrosis	1	Neosynephrin	1	1000	1080	+8.0
4. Ayerza's disease	1	Epinephrin	1	2100	2340	+11.4
		Neosynephrin	1	1630	2240	+37.4
5. Emphysema and coronary sclerosis	1	Neosynephrin	1	4790	5100	+6.5

* Epinephrin = 1:100 epinephrin solution; neosynephrin = 1 to 100 neosynephrin solution; Vaponefrin = Vaponefrin solution; Neo.-epi. = mixture of neosynephrin and epinephrin; Neo.-vapo. = mixture of neosynephrin and Vaponefrin.

In certain instances the change in maximum breathing capacity, that is, the maximum volume of ventilation that the subject could accomplish by voluntary effort,[8] proved a better index of improved pulmonary function than vital capacity. Table 2 gives comparative results in measurement of maximum breathing capacity in 7 cases.

Of the 12 cases of chronic pulmonary disease listed in the tables, all but 2 received appreciable clinical relief from the continuous spray. In 3 instances, the method has since been used successfully by the patients at home for periods of a year or more.

In 1 case, continuous inhalation of neosynephrin vapor brought relief of asthma where epinephrin in any form could not be tolerated. This was B. S. (Table 2), with bullous emphysema and an associated asthmatic dyspnea. Epinephrin hypodermically always produced in this patient severe constitutional symptoms; epinephrin spray caused capillary hemorrhage from the bronchial mucous membranes. After inhalation of 1.5 cc. of neosynephrin a period of asthmatic dyspnea cleared in about 10 to 15 minutes. There was a small increase in vital capacity, and a considerable increase in maximum breathing capacity (Table 2).

Patient G. G. (Table 2) had decided relief from cough following continuous neosynephrin inhalations, though these produced almost no appreciable change either in vital capacity or maximum breathing. This was a woman of 40, with far advanced bilateral tuberculosis and associated pulmonary fibrosis, who was suffering from obstructive dyspnea at rest, which was present constantly, but aggravated by severe spasmodic attacks. The obstructive breathing was both inspiratory and expiratory. Bronchoscopy

showed only marked bronchial spasm, with stiff, contracted bronchi. She had an arterial oxygen saturation of 87%. There was no appreciable change in vital capacity either on continuous spray, or after epinephrin hypodermically. The patient felt subjectively relieved after the spray, however, and was able to raise sputum.

TABLE 2.—MAXIMUM BREATHING CAPACITY BEFORE AND AFTER CONTINUOUS INHALATION SPRAY.

Case.	Diagnosis.	No. obs.	Treatment.	Maximum ventilation, liters/min.		Remarks.
				Before.	After.	
F. H.	Emphysema	1	Neosynephrin, 1 cc.	27.0	37.1	Hypodermic more effective.
		1	Epinephrin, 1 cc.	34.1	45.1	
		1	Epi., hypo., 1 cc.	31.2	48.4	
H. T.	Emphysema	1	Neosynephrin, 1 cc.	32.9	37.3	Hypodermic more effective.
		1	Epinephrin, 1 cc.	28.6	42.2	
		1	Epi., hypo., 1 cc.	34.7	51.9	
M. K.	Ayerza's disease	1	Neosynephrin, 1 cc.	24.0	30.2	Reaction after hypodermic.
		1	Epinephrin, 1 cc.	23.7	45.6	
		1	Epi., hypo., 1 cc.	16.4	62.4	
G. G.	Pulmonary fibrosis	1	Neosynephrin, 1 cc.	..	..	Cough easier after neosyn.
		1	Epi., hypo., 1 cc.	13.9	14.6	
K. B.	Emphysema	1	Neosynephrin, 1 cc.	15.3	19.7	Reaction after any epinephrin.
		1	Epinephrin, 1 cc.	15.3	18.4	
C. G.	Emphysema	1	Neo.-epi., 1 cc.	13.8	20.9	Marked relief from spray.
		1	Epi., hypo., 1 cc.	13.8	21.6	
B. S.	Emphysema	1	Neosynephrin, 1 cc.	23.1	31.1	Reaction after any epinephrin.

The continuous inhalation technique has also been employed successfully in a number of cases of acute bronchiolitis or bronchopneumonia when this has been accompanied by symptoms of obstructive asthma. During the past season several cases of the so-called non-bacterial, or "virus" or "acute interstitial" pneumonia (Reimann[9]) developed such symptoms; in 3 of which the spray was used with marked relief.

One case may be cited briefly. The patient was a young man of 31. Following an acute febrile onset, he became progressively worse for 2 weeks, the major condition being apparently a bronchiolitis with widespread patchy pneumonitis. It extended throughout both lungs, except for a small region in the right upper lobe. Symptoms were fever, weakness, severe racking cough, asthmatic dyspnea, extreme cyanosis. He was in an oxygen tent with an oxygen concentration of 60 to 70%, but still dyspneic and cyanotic. An extra oxygen tank was placed beside the bed, a long rubber tubing connection extending to the vaporizer which was inside the tent. Whenever desired, the spray could be turned on and inhaled without modifying oxygen treatment, and without any extra exertion on the part of the patient. This spray was used, with Vaponefrin as bronchodilator solution, 10 or 12 times a day, with marked relief to dyspnea, asthma, and cough, and no constitutional side-effects. It was of particular value in helping the patient to raise sputum. In the third week, the pneumonia began to resolve, the temperature decreased, and the patient gradually improved.

From the tables, no consistent indication can be obtained as to the relative effectiveness of the various solutions. From clinical observation it appeared that epinephrin 1:100, and Vaponefrin, usually had the strongest action, and neosynephrin the weakest; just as Graeser points out in his recent report.[3] The action of the epinephrin-neosynephrin mixtures seemed to have no special advantages or disadvantages. In some instances, epinephrin hypodermically, 1 cc. of 1:1000 solution, was more effective than any of the sprays (Table 2).

With respect to undesirable side-effects, neosynephrin had none whatever, in any patient, even on prolonged use. Epinephrin not infrequently caused the dryness and irritation of mucous membranes, and occasionally the constitutional side-effects that have been reported with the use of the hand-bulb atomizer and deep inhalation. The continuous inhalation technique did not appear to increase these toxic effects.

From experience thus far obtained, it would appear that the continuous spray technique has two general indications:

1. In severe asthmatic states, to relieve exacerbations of symptoms at intervals through the day; either supplementing ephedrin or hypodermic epinephrin in this respect, or replacing such medication if the subject has become resistant.

2. In cases of chronic fibrosis and emphysema, when they are confined to bed, or on a limited ambulatory régime; for relief of dyspnea, asthma, and cough. In such cases the most effective régime is often to use the spray at regular intervals throughout the day, as well as at other times as needed for acute asthma and cough. A convenient schedule is to inhale the vapor of 0.5 cc. to 1.5 cc. of solution for 4 to 10 minutes (1) on waking in the morning, and before getting out of bed, (2) in the middle of the day, *e. g.*, after lunch, (3) just before retiring at night. Often continuous inhalations of this kind may be supplemented by the use of the hand-bulb vaporizer when the patient is up and about. Our experience corresponds with that of Graeser, that neosynephrin used with the hand atomizer is ineffective.

Epinephrin 1:100 or, preferably, Vaponefrin solution will usually be most effective with the continuous technique, unless there are local or constitutional side-effects; in such instances, continuous neosynephrin inhalations may bring relief.

Summary. 1. A method is described for providing continuous vaporization of solutions of bronchodilator drugs, for use as oral inhalation in asthmatic and emphysematous subjects.

2. This technique often provides more effective inhalation therapy in very ill or dyspneic patients, using 1:100 epinephrin, or Vaponefrin solution than is obtained by the hand-bulb, and with much less effort on the part of the patient.

3. Some patients who were sensitive to 1:100 epinephrin, could

obtain symptomatic relief by neosynephrin 1:100, when this was given by the continuous inhalation technique. The neosynephrin solution, while usually weaker in its action than epinephrin 1:100, was entirely free from undesirable side-effects.

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ON THE QUANTITATIVE RELATIONSHIP BETWEEN CHLORIDE AND SODIUM EXCRETION IN THE URINE.

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Siedeck and Zuckerkandl[8, 9a,b] have found that the ratio of Na:Cl in the urine varied on different days, but insignificantly (0.95 to 1.03) in healthy persons who received ordinary food while staying in bed. Deviations from this value, therefore, as found in several diseases ("serous inflammation") were thought to give rise to far reaching conclusions. They also direct attention to typical differences of the Na:Cl ratio in day and night urine, a matter that is related to our investigations on the different ions in cases of nycturia (Mainzer,[3a,b] Mainzer and Hersch[4a,b]). In 50 day and night urines with normal fluid output and in 50 nycturic urines we determined the sodium, potassium and chloride concentrations from 13 persons in whom there were no other diseases likely to influence the water and salt metabolism. Five of these persons had been for some weeks convalescent from acute infectious diseases. All received the ordinary hospital food with salt at random, and were kept in bed.

Methods. The following methods were used in carrying out the analyses: The chlorides were determined by means of titration (according to Mohr and our own micromethod). Calcium, magnesium and the phosphates were removed (according to the method described by MacKay and Butler; *cf.* Peters and van Slyke[5a]), in order to determine the proportion of Na and K. In the filtrate the total bases were determined (after the method of Stadie and Ross[10]) as sulphates. Following ignition of the urine according to Stolte, Na was precipitated according to the method described by Kramer and Gittleman,[1] modified by Eisenman, as pyroantimoniate and determined iodometrically.

The balance (total bases minus sodium) indicates the potassium concentration (after precipitation of the alkaline earths, as mentioned above). We prefer this indirect method of determining the potassium concentration to the usual direct microdetermination, according to Kramer and Tisdall,[2] since after several years' experience, we agree with the statement of Peters and Van Slyke,[5b] that the latter is not entirely satisfactory. Specific gravity was also ascertained, and the hydrogen-ion concentration determined by means of Michaelis' indicators.

A discussion of our results, as they concern the ratio Na:Cl follows.

TABLE 1.—VALUE OF THE QUOTIENTS Na:Cl IN THE URINE.

Subject.		Number of specimens.	Quotient Na:Cl. Lowest value.	Medium value.		Highest value.	Number of specimens with a quotient Na:Cl = >1.10.	Number of specimens with a quotient Na:Cl = <0.90.
Normal urine	Day	50	0.54	0.99	1.02	1.56	19	23
							42	
	Night	50	0.43	1.04		2.81	16	21
							37	
Nycturic urine	Day	50	0.51	0.92	1.02	1.68	13	29
							42	
	Night	50	0.65	1.12		2.50	21	21
							42	

Table 1 shows that there is no constancy (as held by Siedek and Zuckerkandl[9a,b]) of the ratio Na:Cl. In contrast to these workers, although working under the same experimental conditions, we encountered large variations of this ratio, between 0.43 and 2.81. On the whole, about four-fifths of our results were far from the point of equivalence, namely below 0.90 and above 1.10. This was so with reference to normal as well as to nycturic urines (with day as well as with night urines), between which there did not appear any significant difference, nor did the adjustment of the figures taken from day and night urine (which had been tested separately) produce any results on those lines. This is very clearly shown in Table 2. In more than half of the 100 pairs of urines which were analyzed, the deviation from the ratio Na:Cl = 1 as regards the day and night urines was in the same direction.

TABLE 2.—VALUE OF THE QUOTIENT Na:Cl IN THE URINE.

Subject.	Number of specimens.	Quotient of urine of the day as well as of the night. Lower than 0.90.	Higher than 1.10.
Normal urine	50	13	9
Nycturic urine	50	19	13

The diagram gives a clear picture of the distribution of the different values of the ratio. The abscissa represents the ratio, the ordinate the relative frequency (per 100). In our diagram the figure 0.6 stands for all figures between 0.60 and 0.69, the figure 0.7 for 0.70

to 0.79 and so forth. The diagram is based on the analyses of all 200 urines. We did not take into account figures above 2, since they occurred extremely rarely.

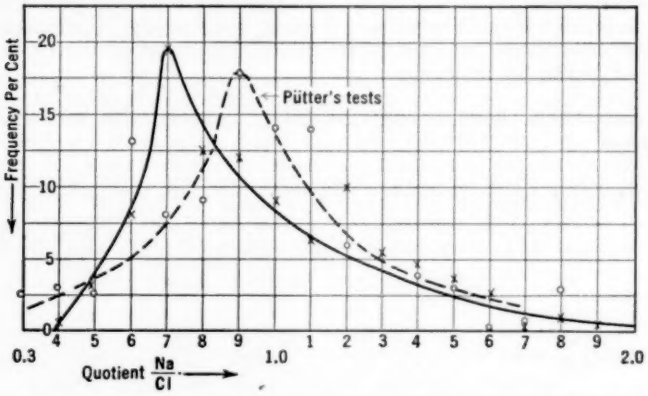

CHART 1.—Distribution of the frequency of the quotient Na:Cl in 200 personal tests (x————x) and in 35 Puetter's tests (o----------o). Abscissa : Quotient Na:Cl. Ordinate : Percentage of frequency.

The diagram shows a regular frequency curve with regard to the different values of the ratio. The distribution seems less regular if normal and nycturic urines are treated separately, in view of the smaller number of results available then, but on the whole both curves follow similar lines. The maximum frequency is not at 1, as should be expected in accordance with the preceding arguments, but between 0.70 and 0.79 (in the diagram represented by the figure 0.7). The curve of frequency declines in both directions, with regard to the higher as well as the lower values, so that the ratio 1 occurs about half as frequently as those around 0.75. The decline of the curve, however, is no symmetrical one, as should conform to the ideal variation curve of accidental deviation from the mean value (binomial curve). The frequency of the occurrence of a certain value of the ratio declines towards the figures below 0.7 much more rapidly than is the case in the increasing values above 0.7. From three-quarters to four-fifths of the chlorides, therefore, are, as a rule, excreted in the urine as sodium salts, the remainder in other compounds. Urines in which greater amounts of chlorides which are combined with other kations are present, show a very rapid decline in frequency, and the greater the amount of such chlorides the more this is so. Urines in which the excreted quantity of Na is larger than four-fifths of the chlorides show a much slower decline in frequency with increasing Na concentration. There are, therefore, under normal conditions comparatively many urines in which considerable amounts of Na are combined with phosphoric, sulphuric and carbonic acid.

It is owing to this peculiar unsymmetrical behavior of the frequency curve that the mean value of the ratio Na:Cl (in all groups which we formed [see Chart]) approaches the value 1, although practically half of the tested urines contain an amount of Na corresponding to but four-fifths of the excreted chlorides or even less.

On an average, in tests carried out over a long period, even according to our analyses, almost equal amounts of Na and Cl are excreted. This contradicts the argument that the low ratio of Na:Cl which we found in contrast to Siedek and Zuckerkandl is produced by an exceedingly high proportion of potassium in the food given by us—most of the calcium and magnesium being excreted through the intestine. Such a disproportion of the ion-supply would have become apparent, in particular, in the total result.

In view of this discrepancy between our results and those of the Austrian workers, we tried to find further analyses of this type in the literature. But it was not without difficulty, however, that we succeeded in finding sufficient material on the determination of the kations in the urine.

The classic paper of Salkowski,[7] still of fundamental importance today, was unfortunately not at our disposal in the original. But we found what we were looking for in 35 analyses* of this kind performed by Puetter[6] on normal urines of a 24-hour period, though carried out from rather a different viewpoint.

The behavior of the ratio of Na:Cl (deduced by us from Puetter's analyses) is clearly illustrated by Table 3.

TABLE 3.—VALUE OF THE QUOTIENTS Na:Cl IN THE URINE. (PUETTER'S TESTS.)

Subject.	Number of specimens.	Quotient Na:Cl. Lowest value.	Medium value.	Highest value.	Number of specimens with a quotient Na:Cl = > 1.10.	Number of specimens with a quotient Na:Cl = <0.90.
Normal 24-hour urine	35	0.31	0.97	1.80	10	14

Puetter's investigations are in accord with our results: 1, the range of variation of the ratio Na:Cl is very large (0.31 to 1.80); 2, in two-thirds of the urines analyzed the ratio is very far from the value of equivalence = 1; 3, the average value taken from all urines very nearly approaches the value Na:Cl = 1.

Even Puetter himself stresses these points. After having reported on the relation between excreted chloride and the amount of kations (deduced from the mean value apparent in 32 analyses, taking also into consideration Na, K and NH_3) he continues: "This proportion is by no means the same in all individual cases, sometimes less chlorine is excreted than should be expected considering the quantity of Na+K, sometimes more" (p. 24). In his opinion this results from the fact "that the ions . . . . largely go their own way in the excretion process . . . . that even if the intake of salt is

* One of the analyses of this series was eliminated (AQ) since it was obtained after the administration of Na-bicarbonate.

as constant as is the intake of *e. g.*, nitrogen, the excretion of the ions and the salts is not at all as constant as that of urea" (pp. 37, 38).

In contrast to the agreement between our findings and Puetter's analyses—insofar as the small number of his analyses permits a conclusion—the curve of frequency of the ratio is symmetrically arranged around the mean value in Puetter's investigations, while in ours it is not. The corresponding curve, given also in the Chart drawn according to the principles mentioned above gives clear evidence of this fact.

The deductions to be drawn from our analyses as regards the ratio of Na:Cl in the urine are, therefore, fully confirmed by Puetter's findings and are included in the following statements:

1. With normal intake of food (the patients remaining in bed in our experiments) the ratio of Na:Cl varies greatly in the urines collected in 12-hour (day and night urines) as well as 24-hour periods (0.31 to 2.81). That means that the chlorides appear in combination with Na-ion and as salts of other kations (K, NH_3, Ca, Mg) and that, on the other hand, the Na-ion is present combined with acids other than hydrochloric (phosphates, bicarbonates).

2. Tests carried out over a long period, however, reveal that under above conditions, Na+ and Cl− are excreted in practically equivalent quantity.

3. With regard to the distribution of the frequency of their occurrence the urines can be grouped in a curve around a maximum value in such a manner that three-quarters to four-fifths are at a great distance from the point at which the excretion of Na+ and Cl− occurs in equivalent quantities (Na:Cl = 1).

Conclusions. In view of these facts, the attempts to draw clinical conclusions from the behavior of the ratio of Na:Cl seems to us justified only insofar as prolonged experimental periods are considered, in accordance with the classic principles of metabolic physiology.

The short-term experiment, which uses ratios obtained on some individual days, only permits of conclusions—if ever—when the amplitudes observed—their extent and regularity of appearance—convince us that they are by no means spontaneous, such spontaneous variations being the rule according to Puetter's and our own analyses.

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ON THE DANGER OF FORCING FLUIDS IN MALNUTRITION.

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SPONTANEOUS edema is a well-known phenomenon of chronic malnutrition. Twenty-three hundred years ago Diogenes Laertius wrote that Heraclitus retired in disgust with mankind to the mountains, lived on vegetables and herbs alone, acquired dropsy and died.[24b] To bring a somewhat similar event to date, Mahatma Gandhi is reported in recent press dispatches to have acquired dropsy in his latest fast.

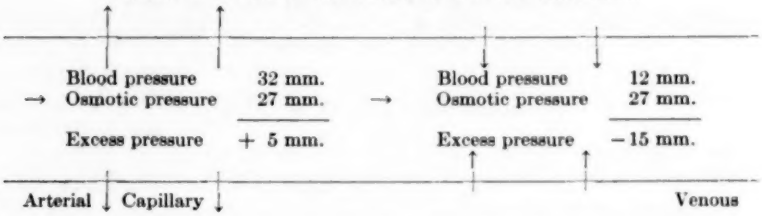
Malnutrition is often accompanied by a dry tongue which may or may not be a sign of dehydration. A diminished urinary output is a more reliable sign of true dehydration than a dry tongue which may be due to mouth breathing. But often without consideration as to the real presence of dehydration, the clinician's first thought is to order large amounts of fluid intravenously. The result may be massive edema, even acute pulmonary edema or eclamptic-like convulsions. The malnourished hypoproteinemic surgical patient is especially liable to such a catastrophe. The mechanism by which such edema may be forced on the malnourished patient is the lowered osmotic pressure within the capillaries brought about by low total plasma protein and plasma albumin accompanying malnutrition.

Our understanding of the mechanism concerned in this edema has progressed as follows:

Starling[19] in 1896 first suggested the relationship of intracapillary pressure tending to force fluid through the permeable membrane wall of the capillary, and osmotic pressure of the blood plasma attracting fluid back into the capillary. Then many cases of edema were recognized as due to malnutrition during the great war, but the mechanism of its production by hypoproteinemia and the resultant lowered plasma osmotic pressure was not generally realized. Next Epstein[7] in 1917 first actually suspected the lowered osmotic pressure of hypoproteinemia as the cause of edema in nephrosis. Others soon applied this idea to cases of nutritional edema, spontaneous cases in America, famine cases in China,[11,12,17,24a,25a,26] and proved again and again the actual presence of low plasma proteins and albumins in such cases. Barker[2] proved the thesis by plasmapheresis experiments in dogs producing massive edema.

The actual mechanism of edema production in the hypoproteinemia of malnutrition may be diagrammed simply modified after Myers:[16]

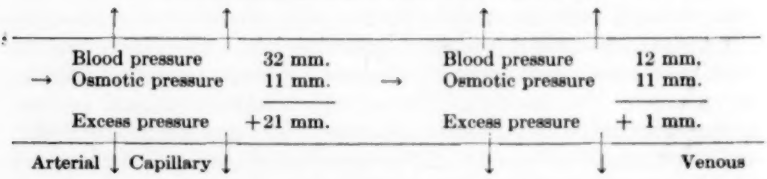
CHART 1.—NORMAL FLUID EXCHANGE IN THE CAPILLARY.



While the above explanation offers the background for the development of edema in malnutrition, other precipitating factors are of the utmost importance. Landis[10] mentions as contributing factors high salt and high fluid intake which will precipitate or increase edema only if both are available, the salt being necessary to fix the fluid in the tissue, and an excess of fluid being necessary to join the salt to form edema.

CHART 2.—EDEMA OF SERUM ALBUMIN DEPLETION.

(1) of nephrosis—excessive loss in urine
(2) of malnutrition—impaired formation or inadequate intake



In clinical practice a combination of malnutrition with unsuspected hypoproteinemia and a dry tongue may seem a prime indication to administer large amounts of glucose in saline. Due to specific protein starvation hypoproteinemia may be present even in the obese patient. The result may be disastrous as in the following case report of an apparently well nourished patient:

CASE 1.—Mrs. J. M., aged 33, entered the hospital on December 17, 1938. Her entrance complaints were anemia and lack of energy of 3 years' duration. Three years previous to admission she was delivered of a normally developed dead baby at term by low forceps, and sustained a third degree laceration, the repair of which rendered intercourse impossible. During her postpartum course she was found to have a pyelitis and anemia with hemoglobin of 30%; red blood cells 2,000,000. While in the hospital she became completely devoid of hair. Only the hair on her head came back sparsely. In the Spring of 1938 a basal metabolic rate was −37%. For the last 3 years she had been having spells of coma which lasted 8 to 9 minutes. For these she had been given glucose and normal saline solution subcutaneously by her home doctor. She had had 5 such attacks in the past year. There was no biting of the tongue or convulsive movements.

There was evidently a considerable psychic factor connected with the episodes of unconsciousness, the patient always staging the spells as her husband was about to enter the house. She had been vomiting for the past year off and on, 3 to 4 times a week the past 2 weeks. The loss of her baby, the impossibility of intercourse, her loss of hair all contributed to her marked melancholy. She was given liver extract, and had been taking an unknown amount of iron and 3 grains of thyroid extract daily for about 9 months, all without improvement.

Family, past medical and social histories were irrelevant. Before we saw her in consultation she had been given an emergency transfusion of 500 cc. of blood and 3500 cc. 5% glucose in normal saline intravenously within 36 hours.

Physical examination after these fluids were given revealed an anemic appearing white female, fairly well nourished who talked slowly and appeared mentally sluggish. Blood pressure was 100/60. The head and neck were normal except for pallor of the mucous membranes, absence of eyebrows and eyelashes, and puffiness of the face. The heart was normal. The pulse rate of 92 on entrance had jumped to 110. There were many moist râles heard throughout both lung fields. The solid abdominal organs were not palpable. There was a pitting edema of both upper and lower extremities as well as over the sacrum. Pubic and axillary hair was scanty.

Laboratory findings: The red blood count, white blood count and hemoglobin were 3,470,000, 10,000, and 55%, respectively. The differential count showed filaments 12%, non-filaments 16%, lymphocytes 59%, monocytes 5%, eosinophils 6%, and basophils 2%. The red blood cells appeared hypochromic in the smear. The Kahn test was negative. On December 19 the non-protein nitrogen was 25 mg., blood carbon dioxide 25 vols.%, blood chlorides 340 mg., blood calcium 8.6 mg., blood cholesterol* 122 mg., total serum protein 6.58 gm., serum albumin 2.91 gm., serum globulin 3.67 gm., albumin globulin ratio 0.8. The low non-protein nitrogen, blood calcium, cholesterol and plasma proteins were probably due to hydremia following 7900 cc. of intravenous fluid in the preceding 36 hours. An uncatheterized specimen of urine was acid, specific gravity 1.015, + albumin, no sugar, acetone or diacetic acid; sediment examination revealed many pus cells, some in clumps, no red blood cells and a few granular casts. The daily urinary output was 150 cc., 750 cc., 350 cc., and then the patient had involuntary urination.

This patient received 7400 cc. of 5% glucose and normal saline in 36 hours. Blood (500 cc.) was given on the day of admission without reaction. Following this the patient developed pulmonary edema and generalized anasarca. On December 20 a duodenal tube was passed and high protein vitamin feedings administered. She was also receiving thyroid, gr. 1, three times daily, cortin, 12 cc. in 2 days, 1 cc. anterior and 0.5 cc. posterior pituitary extract. Her temperature rose to 103.4° on that day, and she expired rather abruptly. Autopsy was refused.

Differential diagnosis: Simmonds' disease is a possibility, but seems ruled out by the absence of any cachexia 3 years following the loss of her hair. Anorexia nervosa is more likely considering the psychic background and hysterical character of her so-called fainting spells. Myxedema must be considered with the low basal metabolic rate of −37%, but she did not have low temperature, slow pulse, coarse features, obesity, high blood cholesterol or response to 3 grains of thyroid extract daily for 9 months. We feel it more likely that the hair loss at the time of her delivery was due to the fever of pyelitis of pregnancy, and the psychic shock of a stillbirth.

Our final diagnoses were malnutrition with edema and acidosis; pul-

* Method of Myers and Waidell in Peters and Van Slyke: The Williams & Wilkins Company, Baltimore, **2**, 506, 1932.

monary edema; terminal bronchopneumonia; anorexia nervosa; pyelonephritis; hypochromic anemia; and question of myxedema.

Comment. It will be noted in this case that the serum protein and albumin were comparatively high (6.58 gm. and 2.91 gm. per 100 cc., respectively) where Moore and Van Slyke[15] assert the usual critical level for the appearance of edema is 5.5 gm. total serum protein and 2.5 gm. serum albumin. One must also bear in mind the predominant rôle of albumin which, being the smaller molecule, exerts the greater osmotic pressure. The loss of albumin, therefore, is of greater import than the loss of other serum proteins. Therefore neither the total protein figure nor the albumin-globulin ratio is of as great importance as regards formation of edema as a low absolute albumin content of the blood plasma. Peters and Eisenman[17] affirm that administration of large quantities of fluid and salt may cause edema to appear at colloid pressures higher than those at which it is usually encountered in nephrosis or plasmapheresis experiments. Youmans[25b] states that in severe cases of nutritional edema the lowered osmotic pressure is the prime factor in the production of edema, but in milder cases with only slight hypoproteinemia secondary factors play an important rôle. The secondary factors precipitating the edema may be posture, the intake of salt and water, environmental temperature, tissue tension, and to this list we might add beriberi. Supported by Weech and Ling,[22] and by Falta and Quittner,[8] Youmans makes the statement, "salt and water are of course necessary for the formation of edema, and within certain limits the giving or withholding of them may cause edema to appear or disappear or modify the amount of edema." These secondary factors often belie the so-called "critical level."

The large amount of salt and water administered before this case was recognized as one of relative hypoproteinemia was undoubtedly the factor precipitating massive edema including fatal pulmonary edema. Weech, Goettsch, and Reeves[23] fed large amounts of salt and water to dogs already rendered hypoproteinemic and found "an augmentation of fluid in the interstitial reservoir" due to a fall in serum proteins enough to cause an average decline of 17 or 20 mm. of water in the colloid osmotic pressure of the serum. They also feel salt and water ingestion causes an augmentation of plasma volume of about 10% and suggest that this increase may be associated with a rise of capillary blood pressure, a further cause for "augmentation of fluid in the interstitial reservoir." The increased fluid volume in the vascular bed and consequent rise of capillary blood pressure constitutes hydremic plethora. It is more probable that the pulmonary edema in our case was caused by the increased capillary pressure due to increased blood volume with left-sided failure. Pulmonary edema is not an occurrence in cases of pure hypoproteinemia as produced in plasmapheresis experiments, nor does it commonly occur in nephrosis.

Weech and Ling[22] gave salt and soda bicarbonate to 2 cases of nutritional edema, and found such feeding caused a marked retention of water and edema, with a retention of chlorides. They concluded the cation sodium was the important element causing the retention of fluid. In one of these patients after a normal serum protein had been restored the edema could not be reproduced by ingestion of large amounts of sodium and water.

Lowenburg and Miller[13] described a nutritional edema in a child due to gastro-enteritis and aggravated by a diet of glucose containing fluids, but no milk, and zwieback (poor in protein). Furthermore, she received 2 hypodermoclyses of 250 cc. of Hartman's solution (which contains NaCl) with consequent development of general anasarca. The child's serum protein was 3.5 gm., serum albumin 2.2 gm. per 100 cc. A high-protein, low-salt diet, and 5% sucrose as a diuretic rapidly reduced the edema and raised her serum proteins.

The following table from Youmans[25b] summarizes the effect of salt added to the diet in cases of nutritional edema:

TABLE 1.

Case.	Added salt.	Weight. Before, kg	Weight. After, kg.	Edema. Before.	Edema. After.	Remarks.
L. E.	9 gm. daily for 4 days	66.3	67.7	0	++++	Legs sore and tender
F. I.	4 gm. daily for 10 days	78.4	80.5	0	++	
	After 8 days of low salt diet	78.8		++	±	
W. J.	10 gm. daily for 5 days	56.5	57.7	+	++++	Legs sore

Another secondary factor precipitating edema in hypoproteinemia is the anemia present in this patient which is known to cause increased capillary permeability. Peters and Eisenman[17] found that in malnourishment with anemia edema appears at higher osmotic pressures than in malnutrition without anemia. Quoting them, "Anemia increases the tendency to edema, and raises the albumin and osmotic pressure at which it may be expected to 4% and 26 mm. Hg, respectively."

The presence of an evidently good state of nutrition as regards the preservation of a good panniculus adiposus, or even obesity, should not throw the clinician off his guard, given a history of imbalanced diet, diarrhea, or vomiting, for even then hypoproteinemia may exist. "The serum protein depletion, like the body protein loss from which it arises, can be retarded and mitigated by the administration of large quantities of fat and carbohydrates; however, regeneration of the serum proteins can be accomplished only when enough protein is added to the diet to permit restoration of the previously wasted body protein. It would seem quite possible under these circumstances for both body protein depletion and hypoproteinemia to coëxist with obesity in subjects who had undergone wasting with

an inadequate protein intake, either for therapeutic purposes or in the course of disease."[17]

The low basal metabolic rate in our case is not to be considered as *prima facie* evidence of hypothyroidism, as it is a common finding in undernutrition, and thyroid therapy in the past had not ameliorated the condition of this patient. Weech[21] quotes Denel and Ling as reporting cases of nutritional edema with basal metabolic rates of -5% to -26% with an average of -16%. One must point out the greater significance of a low metabolic rate in an undernourished patient before edema has occurred. After edema has occurred there is a falsification of standards due to the increased weight of the patient.

Case 2.—Mrs. M. M., aged 58, entered the hospital on December 27, 1937, complaining of diarrhea and vomiting. She said she had lost 45 pounds in weight during the past year, and had been bed-ridden for the past 4 months. Because she vomited most of her solid intake the patient was on a diet consisting chiefly of liquid foods. She had had a diarrhea for 3 weeks prior to admission, with 3 to 6 bowel movements per day. The stools were greenish-gray with no tarry substance or gross blood.

Past history, family history, social history were irrelevant.

Physical examination revealed an emaciated, small female, very ill-appearing but coöperative. There was no pigmentation of the skin. The eyes, ears, nose and throat were normal. The tongue was dry. The right lobe of the thyroid was enlarged, firm and uniform in consistency. Heart, lungs and abdomen were normal. The blood pressure was 80/42, 82/68 and 90/60 on 3 separate days.

Laboratory findings: The red blood cells were 4,640,000; hemoglobin, 55%. A catheter specimen of urine was acid, contained ++ albumin, no sugar or acetone. The microscopic examination of the urinary sediment revealed many white blood cells, many bacilli, and an occasional hyaline cast and red blood cell. A culture of the urine was positive for *B. coli*. The stool examination showed no occult blood. The Kahn and Mantoux tests were negative. The phenolsulphonephthalein test showed 5% excretion in 1 hour. Fluid output varied from 80 cc. to 70 cc. the first 2 days, later increasing to 975 cc. after the intravenous administration of fluids and the disappearance of dehydration.

Roentgen examination of the upper abdominal region revealed a shadow overlying the transverse process of the third lumbar vertebra suggesting a calcium deposit in the right adrenal. Stereoscopic roentgenogram of the chest revealed an old primary tuberculous complex.

Progress. Examination of the gastro-intestinal tract with barium showed a marked duodenal stasis. This was relieved by having the patient lie in the right oblique prone position. She was tube fed, and gradually improved. The diarrhea was stubborn at first, but gradually cleared. She was given 1000 cc. saline intravenously every day for 7 days with 10 cc. cortin. She received 3 gm. salt by mouth in capsules daily. A marked peripheral edema developed. This improved under diuresis by mercupurin and acid salts. The blood pressure increased from 80/42 to 124/70. At the height of her edema the patient developed eclamptic-like convulsions. She also developed an acute cystitis while in the hospital which was treated and improved. She was discharged against advice when a jejunostomy was proposed to enhance protein feeding. The vomiting together with the edema and convulsions continued at home. The patient finally died following a convulsion 3 months after discharge. A serum protein obtained at the patient's home showed a further drop after improvement in the hospital. Autopsy could not be obtained.

TABLE 2.—DATA IN CASE 2.

Date.	Dec. 28.	29.	30.	31.	Jan. 1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	Feb. 22.
Fluids i-v, cc. saline .	2000	2000	500 blood	1000	1000	1000	1000+ 500 of blood	1000	Edema noted											
N.P.N.	105.6	..	..	108.08	..	..	67.44	..	..	..	49.98	..		..	44.79	..	60			
Blood chlorides . .	330	..	..	410	..	..	..	430	..	..	470	..		..	440					
Total proteins . .	..	..	..	..	..	..	..	..	..	..	..	4.887		..	6.233	..	5.888	..	..	5.035
Serum albumin . .	..	..	..	..	..	..	..	..	..	..	..	2.373		..	2.148	..	2.342	..	..	1.719
Serum globulin . .	..	..	..	..	..	..	..	..	..	..	..	2.514		..	4.085	..	3.546	..	..	3.316
A/G ratio . . .	..	..	..	..	..	..	..	..	..	..	..	0.94		..	0.5	..	0.65	..	..	0.51
Weight, pounds . .	..	..	..	..	68	..	..	..	89	89.5	87.5	87.5	86.5	85.5	84.5	76.5	75	74.5	74	

Diuretic régime started

Final diagnoses: Addison's disease; edema of hypoproteinemia and malnutrition; primary pulmonary tuberculous complex; chronic pyelitis; acute cystitis; hypochromic anemia; mesenteric pedicle compression with duodenal stasis; non-toxic nodular goiter.

Comment. This case points out the danger of salt and water therapy pushed too far in Addison's disease. While there was marked rise in blood pressure, blood sodium chloride and the general clinical improvement usually seen in Addisonian crisis on this type of therapy anasarca and eclamptic-like convulsions suddenly intervened. The analogy between this patient's convulsions and those of eclampsia is striking in view of the newer knowledge concerning the cause of the latter. Strauss[20] observed that true toxemia of pregnancy often accompanied by eclamptic fits was associated with hypoproteinemia with a significant gain in weight, edema and hypertension when soda was administered either as the chloride or bicarbonate. Arnold[1] also attributes eclampsia with its convulsions to fluid imbalance. Herden[9] believes that protein stabilization treatment has dealt with fundamental factors in the prevention of eclampsia. de Snoo[18] states that salt retention in the tissues is the true cause of eclampsia which is another way of indicting fluid imbalance.

The persistence of edema in this patient after improvement in her serum proteins may be partly attributed to another secondary factor in the cause of edema; namely, tissue distention once edema has been extreme. Weech[21] again states that in malnutrition the resistance of the connective tissue network may be impaired. A chronic distention of this network therefore may account for persistence of edema after the plasma osmotic pressure has been restored to normal.

The same author is authority for the statement that the blood cholesterol is normal in nutritional edema as contrasted to nephrosis. It will be noted that the blood cholesterol was within normal limits in our patient.

Case 3.—Miss A. S., aged 38, a well-nourished female, was brought to the hospital with a diagnosis of acute intestinal obstruction. At exploration the day of admission a carcinoma of the hepatic flexure was disclosed. A lateral anastomosis was done. The patient was given 2000 cc. of 5% glucose in saline intravenously immediately postoperatively. The following day she was given 4000 cc. of 5% glucose in saline solution intravenously. At that time it was noted that she was developing generalized edema.

Laboratory findings: Total serum protein determined at the onset of edema 2 days after entry was found to be 4.711 gm., the serum albumin was 2.820 gm., and the serum globulin was 1.891 gm. The A/G ratio was 1.4.

The patient was given blood transfusions of 500 cc. each on the second and fourth postoperative days. On the fifth postoperative day all clinical edema had disappeared. She expired on the seventh postoperative day. At autopsy, peritonitis was found to be cause of death.

Case 4.—Mrs. F. S., aged 34, was a patient in the hospital for 10 months. She had a recto-vaginal fistula, attempts for the repair of which had been made on two occasions. Following her second operation she was given 1000 cc. of 5% glucose in normal saline daily for 10 days. She developed an edema over the sacrum and a peripheral edema.

Laboratory findings: Total serum protein at the onset of edema was found to be 5.3 gm., the serum albumin was 3.3 gm., and the serum globulin 2 gm. The A/G ratio was 1.6.

The intravenous injections of 5% glucose in saline solution were discontinued with the onset of the edema and 5% glucose in distilled water was substituted. On this regimen the edema gradually subsided.

Comment. More warnings have been sounded in the medical literature concerning the danger of over-pushing intravenous fluids in postoperative cases than in medical cases of malnutrition. Coller, Frederick, Dick and Maddock's[5] monumental work on water balance lays the foundation for proper treatment of such cases. They have pointed out the necessity of a judicious choice between glucose in distilled water and saline solution administration when further administration of saline infusion may result in salt and water retention. It is interesting to note that the edema of Case 3 disappeared on administration of blood transfusions; and in Case 4 on switching from saline solution to 5% glucose in distilled water.

Meyer[14] reported a patient who developed massive, fairly generalized edema after an abdominal operation which could be easily and logically explained upon the basis of undernutrition, protein loss through purulent drainage, and dilution of serum proteins by the administration of large quantities of salt and water in the form of normal saline. He points out the possible danger of causing pulmonary edema in pushing fluids in such cases. Beard and Blalock[3,4] have also warned of the same danger of edema by postoperative fluid therapy diluting the serum proteins.

The authors have had no experience with the intravenous administration of amino-acids, but the method recently reported by Elman and Weiner[6] offers great promise of being an ideal solution of the necessity to correct the serum protein level before dehydration can be safely corrected in these cases.

Conclusions. 1. A low fluid output is a better sign of dehydration than a dry tongue.

2. The hypoproteinemia of malnutrition constitutes a contraindication to the administration of large amounts of salt and water parenterally, despite the fact the patient may appear to be dehydrated.

3. The serum proteins must first be reëstablished to normal before attempting to correct dehydration or massive edema, fatal pulmonary edema, or eclamptic-like convulsions may supervene.

4. Too much salt and water intravenously in cases of malnutrition precipitates an edema already potential by reason of the lowered osmotic pressure of hypoproteinemia. Hydremic plethora with its increased intracapillary pressure further conditions the organism for the precipitation of acute pulmonary edema.

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SEASONAL VARIATION IN THE WATER CONTENT OF THE RESPIRATORY TRACT.

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Seasonal variation in the susceptibility of the respiratory tract to infection in northerly climates is well known. Hitherto, most research on this problem has been directed at the pathogenic organisms and the pathologic processes involved. There is little information pertaining to the reason why the respiratory tract is more easily invaded by these organisms at certain seasons of the year. The present work was undertaken with the idea of measuring, at different seasons of the year, something which might be considered as an index of the function of the respiratory tract. The work was done on animals housed under conditions of heat and humidity which may be considered somewhat similar to those of the average human population of this district.

The water content of the trachea and of the bronchial and alveolar regions of the lungs was measured as an index of the function of these tissues. It was concluded on theoretical grounds and later proven by experiment, that the water content of tissues lining the respiratory airway must be finely adjusted. The cells lining the respiratory airway are continuously subjected to the passage to and fro of air, air which is warmed to body temperature and which

usually enters the body with insufficient moisture to saturate it at body temperature. The air passages are thus constantly fanned by dry, hot air. Some moisture is added to incoming air as it passes through the nasal cavity. If not sufficient, then further water must be evaporated from the cells lining the trachea, bronchi and smaller air passages. If any water so removed were not soon replaced, these tissues would dry up and become lifeless. That such does not occur is seen in the fact that animals and man may live for considerable periods—possibly indefinitely—when air is side-tracked from the nose and enters by way of a tracheotomy tube.

On the other hand, it is equally as important that too much secretion of water by these cells be prevented. If such occurred, the very fine air passages might become filled with a watery medium and the animal or person drown in its or his own secretions.

On these theoretical grounds, we concluded that there must be a fine adjustment in the water content of pulmonary tissues. If such were so, then one might find a relatively constant water content in these same tissues. This was determined experimentally to be the case. Being reasonably certain that water content could be taken as an index of function of these tissues, we proceeded to measure water content over a period of 1 year.

Method. The object of the procedure adopted was to measure the water content of different regions of the respiratory tract of laboratory animals under conditions which might be regarded as nearly normal as possible. The animals were housed in quarters wherein the temperature and humidity were the same as those to which persons working in the laboratory were exposed. They were allowed to drink and eat as they wished. The white rats were fed Purina Fox Chow Checkers; the guinea-pigs, alfalfa and fresh vegetables; and the cats, milk, bread and meat. The animals were killed without anesthesia by a light, stunning blow on the head followed by severing the cervical spinal cord with snippers. The thorax was then quickly opened, the trachea freed at the larynx and separated down to and including the lungs, keeping the tract free of as much blood as possible. Any adherent tissue was then removed and the whole divided into three parts. The trachea was one part. The distal third or half of each lobe of the lung constituted the second fraction which was termed the distal part or distal lung. The remaining parts of the lung were called the proximal part or proximal lung. A diagrammatic representation of these separated fractions is given in Figure 1. As described below, there was found to be a physiologic as well as an anatomic difference between the proximal and distal parts of the lung.

The separated fractions were quickly placed in separate, small, cleaned, dried and weighed weighing bottles with ground glass stoppers and the moist weight determined to the nearest 0.1 mg. They were then placed in a drying oven at 90° C. for 60 to 100 hours with the stoppers ajar. The stoppers were then inserted, the bottles cooled to room temperature and the dry weight ascertained. From these values the percentage of water in the original moist weight of tissue was calcula ed.

Results.—It was first necessary to establish whether the crude separation of the lobes of the lung gave fractions of significantly different water content. If such were not the case there would have

been little incentive to continue dividing the lung. A representative comparison of the respective percentages of water in the proximal and distal fractions of 11 young, 170-gm. rats is shown in Table 1. It will be noted that in all of the animals, the proximal part contained more water than the distal part. The mean difference was 1.6% of water with a standard deviation of 0.48 which is indica-

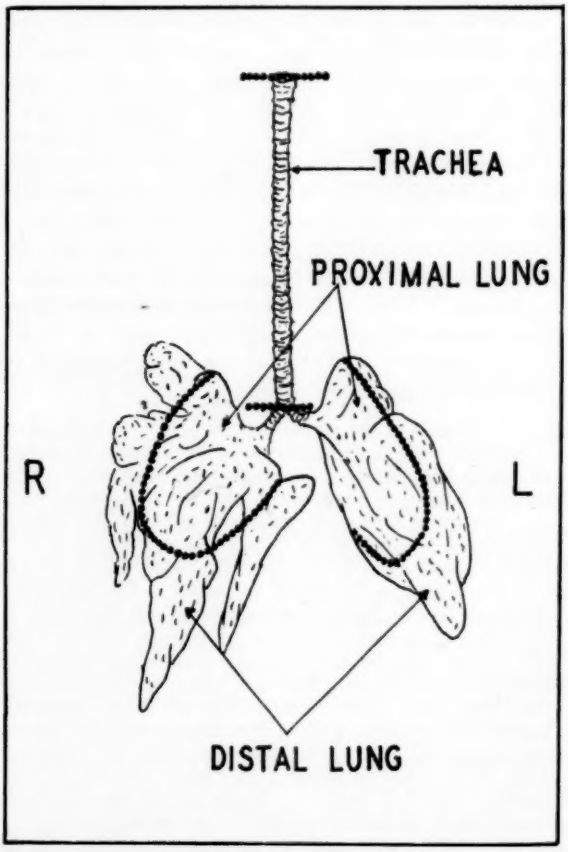

FIG. 1.—A diagrammatic representation of the separated fractions of the respiratory tract of albino rats.

tive of a statistically significant difference.[3] In certain other experiments, changes in water content were noted to affect one fraction and not the other. Hence it may be concluded that there is a significant physiologic difference in the two fractions of the lung as separated and this separation was thus used in subsequent work.

The Constancy of Lung Water. It has been suggested above that the water content of tissues composing the trachea and lungs must

be finely adjusted. If such were so, one might expect to find a relatively constant amount of water in such tissues. To investigate this, water percentages in representative groups of albino rats, guinea-pigs and in 2 cats were analyzed statistically and have been

TABLE 1.—THE WATER CONTENT OF A PROXIMAL AND DISTAL DIVISION OF THE LUNGS OF YOUNG RATS.

Rat No.	Per cent water. Distal part.	Proximal part.
78	78.8	77.2
79	77.9	77.9
80	78.8	77.0
81	82.7	80.2
82	78.5	77.3
83	81.3	78.2
84	79.0	77.8
85	78.8	77.4
86	79.6	77.7
90	78.7	78.3
137	78.2	76.4
Mean	79.2	77.6
Standard deviation	1.4	0.91
Standard error	0.40	0.26

presented in summary in Table 2. All values in each of these groups were obtained at the same season of the year and at times when abnormal variation, to be described later, did not occur.

Pearson's coefficient of variation[3] was used as a means of estimating and comparing the relative variation. Pearson's coefficient is

TABLE 2.—VARIATION IN THE WATER CONTENT OF THE RESPIRATORY TRACT OF ALBINO RATS WITHIN A GIVEN SEASON.

Value.	Per cent water. Trachea.	Proximal part.	Distal part.	Whole tract.
24 Albino Rats.				
Mean	74.3	78.7	79.5	78.8
Standard deviation	3.6	0.91	0.89	0.73
Pearson's coefficient of variation	4.9	1.2	1.1	0.93
15 Guinea-pigs.				
Mean	64.2	78.4	80.1	76.9
Standard deviation	12.2	1.3	3.4	3.8
Pearson's coefficient of variation	19	1.6	4.3	4.9
2 Cats.				
Cat 1				81.3
Cat 2				81.8

the standard deviation divided by the mean and multiplied by 100; or, in other words, it is the standard deviation expressed as a percentage of the mean. In rats, the coefficient of variation of values for the water content of the whole respiratory tract and of the proximal and distal parts of the lung was remarkably constant at a value of about 1. The coefficient for the rat trachea was a good

deal higher, being 4.9. In guinea-pigs there was little variation in the water content of the distal part of the lung but considerable variation in the proximal lung and in the trachea.

For comparative purposes, variations in the water content of a number of tissues were collected at random from reprints on hand and Pearson's coefficient calculated. These comparative values have been given in Table 3. It will be noted that in general the coefficient is lowest for the lungs and that the only other body tissue approximating this constancy is the gray matter of the brain. On the other hand, the water content of the trachea is quite variable, relative to that of other body tissues. The coefficient of variation of other body constituents, for example lipids,[1] runs from 15 to 40 or more.

TABLE 3.—PEARSON'S COEFFICIENT OF VARIATION OF THE WATER CONTENT OF SEVERAL BODY TISSUES.

Tissue.	Animal.	Pearson's coefficient.
Respiratory tract (Table 4)	Rat	0.99
Distal lung—Tb. II	Rat	1.1
Proximal lung—Tb. II	Rat	1.2
Distal lung—Tb. II	Guinea-pig	1.6
Brain—gray matter (8)	Man	1.6
Uterine mucosa (5)	Pig	2.5
Brain—white (8)	Man	3.1
Trachea—Tb. II	Rat	3.6
Proximal lung—Tb. II	Guinea-pig	4.3
Gingival tissue (4)	Man	5.5
Teeth (2)	Man	18.7
Trachea—Tb. II	Guinea-pig	19.0

It is obvious from these remarks that the water content of the lungs is remarkably constant. These results would appear to substantiate the suggestion that the water content of lung tissue is under a nice control. Since the wide variation in guinea-pigs was found due to a bimodal distribution of results, the reason for which was not apparent, it was decided to continue the work using albino rats only.

The Effect of Age. The present work was begun with a group of older, mature albino rats weighing 300 gm. and continued with young rats weighing 150 to 200 gm. bred from the original stock. To ascertain if there was any difference in the water content of the respiratory tract of these two groups, results in 19 of the older animals were compared with results in 11 of the young rats, the water content being determined in both groups during June and July. There was no significant difference in the water content of the whole respiratory tract nor of the distal part of the lung but the trachea of the young rats contained slightly, but significantly, more water and the proximal part of the lung slightly but significantly less water than the corresponding parts of the older rats. The younger rats were used when they had reached at least 150 gm. in weight for the remainder of this work.

Seasonal Variation. As data accumulated, it became obvious that the water content of the respiratory tract was varying at certain seasons of the year. When the results for the whole respiratory tract were plotted according to the date on which they were obtained it became obvious that during the first cold spell of the autumn in September and October (early) when outside temperatures fell periodically to 60 to 65° F. and the laboratory had not yet been placed on regular and uniform heating, a considerable proportion of the water values were above normal. An opposite tendency to be below the normal range was seen in the results obtained from January to March after the animals had been exposed to a prolonged period of dry heat from a hot water heating system. This inference was drawn from the plotting of 120 determinations of the water content of the whole respiratory tract fairly evenly distributed over 11 months of the year.

In order to demonstrate these results, the mean of the entire group was calculated and was found to be 78.3% of water with a standard deviation of 1.16% of water. The results were then divided into periods of 5 weeks consecutively, such groups containing at least 10 animals. The number of animals in each 5-week period with water contents above the mean plus the standard deviation of the entire group was calculated. Also the number of animals with values below the mean minus the standard deviation was found and in each case the numbers were expressed as a percentage of the entire number of animals of the individual group. These percentages of cases above or below the range of the mean plus and minus its standard deviation were then plotted according to season in Figure 2.

The range of the mean plus and the mean minus the standard deviation includes two-thirds of all expected values. Of the remaining one-third of values, a half or one-sixth would be expected to lie above this range and one-sixth below it. Or 16.7% of a given distribution may be expected to lie above the stated range and 16.7% below it. This statistically *expected* variation is indicated in Figure 2 as a dotted area. Any variation beyond this dotted zone would not be expected in a random distribution of results. Yet in September and early October, 45 to 67% of values were above the range, given 3 to 4 times the expected variation above the range. Also in January, February and March, 50% of values were below the range showing again 3 times the expected variation below the range.

To prove that these changes graphically illustrated in Figure 2 were statistically significant, the data were divided into three groups. Group A included results obtained in September and early October, Group B those in January, February and March and Group C all other values. An analysis of the differences between these groups was then made and the results are given in Tables 4 and 5.

Table 4 presents data which demonstrate that when the unusual results in the early autumn and mid-winter are subtracted from the total cases, there remains a group of 71 cases in which the coefficient

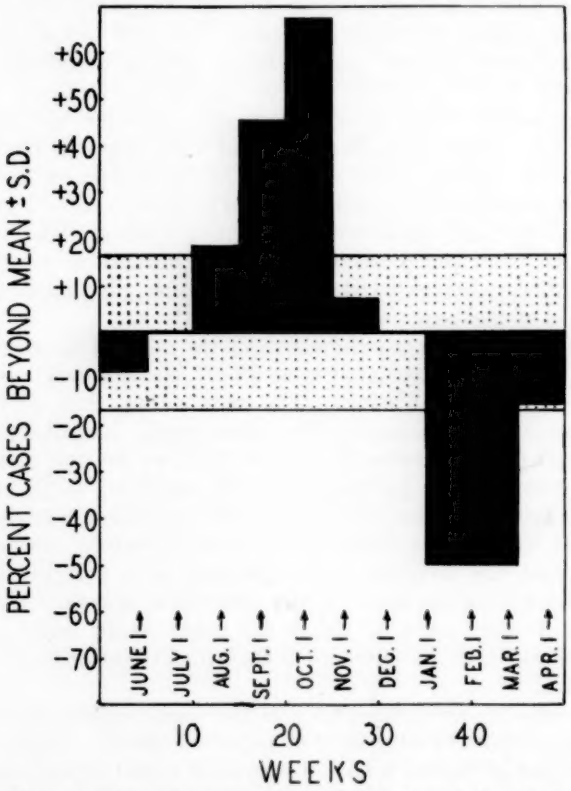

FIG. 2.—The percentage of cases, grouped in 5-week periods, showing more or less water than the range included by the mean plus and the mean minus the standard deviation. The dotted area represents the expected variation.

of variation is only 0.99. This demonstrates again that except for these two seasons, the water content of the rat respiratory tract remains exceedingly constant. In early autumn there was a rise in

TABLE 4.—A STATISTICAL ANALYSIS OF DATA, GROUPED ACCORDING TO SEASON, ON THE WATER CONTENT OF THE ENTIRE RESPIRATORY TRACT.

Group.	No. of cases.	Season.	Mean.	Standard deviation.	Standard error.
A	35	Sept.–Oct.	79.7	0.88	0.16
B	14	Jan. –Mar.	77.2	0.93	0.25
C	71	All others	78.2	0.77	0 092

the water content of the respiratory tract from a mean of 78.2% to a mean of 79.7%. The mean difference of 1.5% of water was calculated to have a standard deviation of 0.19; the mean difference

was thus 7.9 times its standard deviation which is indicative of an overwhelmingly significance (Table 5). In the mid and late winter season, there was a fall in the water content from 78.2 to 77.2%, giving a mean difference of 1% of water which had a standard deviation of 0.27, the mean difference being 3.7 times its standard deviation and again overwhelmingly significant.[3] And, of course,

TABLE 5.—THE SIGNIFICANCE OF MEAN DIFFERENCES BETWEEN SEASONAL GROUPS OF TABLE 4: GROUP A—SEPT.-OCT.; GROUP B—JAN.-MAR.; GROUP C—ALL OTHERS.

Groups.	Mean difference.	Standard deviation of mean difference.	Mean difference / Standard deviation.
A–C	+1.5	0.19	7.9
B–C	−1.0	0.27	3.7
A–B	+2.5	0.30	8.3

there was a similar significant difference between the results in early autumn (Group A) and those in winter (Group B). These data conclusively demonstrate that there is a significant increase in the water content of the whole respiratory tract of white rats in early autumn and a significant decrease in winter.

Seasonal Variation and Fractions of the Respiratory Tract. An analysis of the data for each fraction of the respiratory tract was made in a manner similar to that for the whole tract which has been

TABLE 6.—THE SIGNIFICANCE OF THE EFFECT OF EARLY AUTUMN ON THE PER CENT WATER OF THE VARIOUS FRACTIONS OF THE RESPIRATORY TRACT.

Fraction.	Mean difference from normal.	Standard deviation of mean difference.
Trachea	+2.8	1.2
Proximal lung	+2.0	0.37
Distal lung	+1.0	0.47

presented above. The effect of early autumn on the several fractions is analyzed in Table 6. All fractions of the respiratory tract were found to have significantly more water in the early autumn. The greatest increase occurred in the trachea, then in the proximal part of the lung and the least increase in the distal part of the lung.

TABLE 7.—THE SIGNIFICANCE OF THE EFFECT OF MID-WINTER ON THE PER CENT WATER OF THE VARIOUS FRACTIONS OF THE RESPIRATORY TRACT.

Fraction.	Mean difference from normal.	Standard deviation of mean difference.
Trachea	−4.1	1.4
Proximal lung	−0.5	0.39
Distal lung	−1.9	0.24

A similar analysis of the water content of the fractions in winter revealed that there was a marked decrease in the water content of the trachea and distal fractions of the lung with no significant change in the proximal part (Table 7). Unfortunately, only 14 animals

were examined in the winter and the authors hesitate to attach too much significance to the differences between the distal and proximal parts of the lung.

Discussion.—The experimental evidence presented in this report proves that at most times of the year the respiratory tract of the albino rat contains a remarkably constant percentage of water. At two seasons, during the first cold spell of the autumn (to which the animals were exposed in an unheated building) and during the winter months in a hot water heated building, there occurred significant, abnormal changes. These changes invite the drawing of a corollary between them and the well-known preponderance of respiratory infections at the same seasons of the year. The comparison is more significant when it is recalled that these rats were housed under conditions which were probably similar to those under which the larger part of the human population in this district existed, with the exception that the rats did not go out-of-doors. The incidence of pneumonia reached its peak in Kingston at the time that these rats had the lowest water content in their respiratory tracts. It is a little more difficult to estimate the incidence of the common cold, bronchitis, laryngitis, and so on, since these are not reportable diseases. However, the absentees of medical students from lectures reached peaks corresponding to the times of abnormal change in the water content of the rat lungs; at the same times the common cold and an epidemic of "influenza" were prevalent in Kingston and the data are offered for what they may be worth.

The present work would therefore suggest the possibility that infection of the respiratory tract may have as an etiologic factor, in addition to those known or believed to exist, a possible change in the physiology of the respiratory tract itself. It would appear that sudden chilling may alter the normal physiology of the respiratory tract and this possibility is being further investigated. Hot, dry air in artificially heated buildings may tend to dry the lung tissues to some extent and this alteration in lung physiology may account in part for respiratory infection in mid and late winter. *Apropos* of this, the observations of Rabinowitch[6] and Urquhart[7] are of interest: they state that respiratory infection is relatively uncommon among Canadian Eskimos who spend their winters in igloos in which the air would be probably fairly well saturated with moisture.

Summary. The percentage of water in the lungs of guinea-pigs and albino rats was found to remain remarkably constant. Pearson's coefficient of variation averaged about 1. In the albino rat, a significant increase in the water content occurred during the first cold spell of the autumn weeks and a significant drying of the respiratory tract took place in the winter in animals housed in a building heated by a hot water system. These changes affected all parts of the respiratory tract, especially the trachea and the proximal part of the lung in the autumn and the distal part of the lung in the

winter. The correspondence of these seasons to those in which respiratory infection is epidemic has been noted.

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DISEASE AND THE NEGRO:

THYROID INVOLVEMENTS.

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FROM the relatively sparse literature on thyroid disease in the negro the idea was obtained that the condition was regarded as uncommon. We have investigated the situation naturally including a comparative study of the same condition among whites. Our hospital admissions are from a limited territory, representing families of employees of the Tennessee Coal, Iron and Railroad Company. For a number of years the relative proportion of whites and negroes in the employ of this company has been about 60% whites and 40% negroes. On January 1, 1938, there were employed 14,074 whites and 11,796 negroes. With this in mind, it is interesting to note that since the Employees Hospital was opened in November, 1919, to December 1, 1937, there have been 96 operations for thyroid disease in negroes against 133 operations for the condition in whites. Of the negroes, there were 8 males (9 operations) and 83 females (87 operations). Of the whites, there were 22 males (23 operations) and 101 females (110 operations).

Although the cases reported here do not comprise a very large group it is believed that they fairly represent similar conditions among the colored population of this County and State. They certainly present a definite comparison of the patients admitted to the Employees Hospital over a fixed period. It is logical to conclude that in Alabama thyroid disease is as relatively common in negroes as in whites.

The estimated population in the State of Alabama for the year 1937 was as follows: white, 1,857,522; negro, 1,021,440. A similar estimate for Jefferson County was: white, 295,000; negro, 182,100.

The normal capacity of the Employees Hospital is 310 beds and the yearly admissions, over a 10-year period, have been as follows:

TABLE 1.—WHITE AND NEGRO HOSPITAL ADMISSIONS.

Year.	Whites.	Negroes.
1928	4122	2701
1929	4034	2793
1930	3989	2593
1931	3782	2263
1932	3400	2005
1933	3516	2267
1934	3983	2353
1935	3816	2223
1936	4008	2418
1937	4668	2833
Ten-year total	39,318	24,449

Practically all the variations of this disease have been seen except the true Riedel's tumor. The cases were classified as follows:

TABLE 2.—DISTRIBUTION OF THYROID CASES.

	Negroes.		Whites.	
	Females.	Males.	Females.	Males.
1. Diffuse toxic thyroids	34	3	49	15
2. Diffuse non-toxic thyroids	3	0	2	0
3. Nodular toxic thyroids	27	3	44	5
4. Nodular non-toxic thyroids	20	3	14	2
5. Carcinoma	2	0	1	1
6. Suppurative thyroiditis	1	0	0	0
Totals	87	9	110	23
Grand totals	96		133	

		Place of birth.			
		Alabama.	Georgia.	Mississippi.	Louisiana.
Negro males (9 operations)	8	8			
Negro females (87 operations)	83	72	6	4	1

Of the negro males, 6 were married and 2 were single. Of the negro females, 79 were married and 4 were single. The age incidence was interesting and according to the decades of life was as follows:

TABLE 3.—THYROID CASES ACCORDING TO SEX, COLOR AND AGE GROUPS.

	Second decade (11–20).	Third decade (21–30).	Fourth decade (31–40).	Fifth decade (41–50).	Sixth decade (51–60).	Seventh decade (61–70).
White males	1	4	2	12	3	1
White females	14	36	41	13	6	
Colored males	1	4	3	1		
Colored females	5	25	45	12		

One of the most interesting observations of these thyroid cases among negroes was their attitude toward the condition and towards the treatment, including operation. Most had postponed seeking medical aid much longer than the white patients with a similar complaint.

As observed by other workers, this favors a secondary toxic condition in a thyroid which has been "out of balance" for years. It may also account for the fact that many of the negroes have advanced toxicity with a corresponding circulatory damage when first seen. The negro's delay and apparent unconcern is detrimental because it brings him help only late in the disease. It may be that this same attitude of unconcern about his operation and other treatment is a definite aid to recovery, for he is very skeptical about everything he is told and is inclined to only believe just so much as he thinks will be to his own benefit.

The negro also has a peculiar courage when once he has accepted advice about surgical procedures; and this, together with his helpful coöperation, goes a long way towards recovery.

Among other things of interest noted in comparing the negroes and the whites following thyroidectomy was the short stay in the hospital by the majority of negro patients following operation.

It was also noticeable that their convalescence seemed easier as well as more rapid and that the negroes required very little medication such as morphine and other narcotics and sedatives.

We are of the opinion that these so-called "southern Negroes" are likely to present a different picture and different problem from their brothers, who have moved to Chicago, Detroit or any of the other larger cities of the North and East. This is, no doubt, true because the southern negro's point of view (attitude towards disease) is different from the type of negro just mentioned. After several years away from his relatives and friends, both white and black, he, in the northern metropolis, finds for himself that the body is subject to many ills, the names of which he had never heard in his southern home. For the first time he learns that he may have a gastric ulcer, or cholecystitis or even a goiter. With this change of attitude and with this increase in knowledge, he presents himself with the condition which his better informed white friend has previously experienced.

It has interested us to observe that among the diseases which many clinicians, among them Moschcowitz,[3b] believe due to psychogenic causes hyperthyroidism appears with equal frequency in both races. This group is held by some to consist of thyrotoxicosis, gastric and duodenal ulcer, mucous colitis, essential hypertension and cardiospasm, with other diseases bordering on the fringe of these complexes.

As to gastric ulcer in the negro race, in our experience it is rarely found and still more rarely complained of. This is confirmed by the infrequency of Roentgen ray examinations here investigating this condition. The reasons for this state of affairs, discussed elsewhere,[5] are in effect the same as those which govern the appearance of mucous colitis in this race. So far as that entity is concerned we can say with truth that we have yet to see the disease appear in a

negro's body in the same shape and significance as it does in our own race. If such events ever take place they have been concealed from our notice.

Cardiospasm we have never observed in a negro; we cannot recall ever having seen a negro of these parts who complained of either the subjective or objective symptoms of this disease. The name is foreign to their vocabularies.

Arterial hypertension is an actuality in the negro race and we have reason to believe that it appears more frequently in this race than in the white and that its development comes about earlier in the life of the victim. Not only are high blood pressure readings common events but death from cerebral hemorrhage and the findings of the post hemiplegic state are frequent occurrences among the negroes of the deep South. At the same time complaints due to this condition are not so frequent in the black man and woman as in their white companions. We see the elevated blood pressures, and the scars from the hemorrhage into the brains of these people but we hear far less of the vertigos, the headaches, the roaring in the ears which come to plague the lives of so many Caucasians.

Many negroes are found hard at work with blood pressures at an extremely high figure and are surprised to learn what their physician has discovered. Not only surprised but little, if any, concerned. We have seen no reason to suppose that they ever entertain any sequential ideas as to high blood pressures and a death from apoplexy. They never offer to change their way of living in any manner and resent universally the idea of refraining from hard labor on account of any such discovery. So much for these diseases as a group.

It would appear to us that in nurturing a disease (hyperthyroidism) which first became prominent in white women the negress made use of her unwonted powers of imitation. The mere appearance of a swelling of this description is such as to make an undying impression upon all who have seen it. It remains in the recollection of the onlooker after all other memory of its possessor has departed. In a way, we can say that the owners of these lesions have them on parade. They are proud of them, make the most of the opportunities to have them on exhibition and are not slow to advertise the special privileges in life to which they consider themselves entitled as a result of this achievement. This attitude has been remarked upon more than once among our cleverer writers of fiction, even if it has not as yet crept into our technical literature. The persistence with which the symptoms of this disease return again and again gives warning of the tenacity of purpose with which their possessors cling to their unusual gift.

To all the motives which underlie this as other forms of disease the negress turns a bright and curious eye. Knowing about the whites as the negro race does—our habits, personalities and inten-

tions—we may be sure that no sooner had a white woman used this disorder for making profound changes in her daily existence, than the negresses of the community became aware of the procedure. From knowledge to purpose and then to achievement are but narrow steps indeed.

The state of the knowledge of this disease in the negroes of these parts is only fair, not comprehensive. They always, so far as we have observed, call it a "goiter," and after the news has been conveyed to them of what ails them frequently inquire if it is an "inward goiter" as differentiated from an "outward goiter." We have never heard them use the word "thyroid" or "hyperthyroidism." Details of symptoms seem to be unknown to them. They have become aware that certain events follow in those who have contracted this malady. As a rule, they defer all forms of treatment until the growth is far advanced.

The results of this racial comparison in the occurrence of thyroid disease in our opinion casts doubt upon theories advanced to explain its appearance in the white race. Moschowitz[3a] and others have defined a type of individual in which the sickness is apt to develop. This personality possesses certain physical and intellectual stigmata; to such a degree, in fact, that the observer might be warranted in predicting when and where such a catastrophe might make its presence known. We cannot help but feel that much of what we have deduced from becoming familiar with the negro of the deep South contravenes many of these ideas. The white woman destined to fall a prey to this misfortune has been portrayed as a high strung, nervous, self centered introvert. We have no such types among the negresses who have come under our care for this form of malady. The description of such characters as met with among Caucasians display qualities physical and mental which are not encountered in the more primitive race. Aside from the exophthalmos which is so commonly found among the negroes and which is one of their racial insignia, we have searched in vain for the other well known evidences. Apart from the protruding eyes, the character of the negro as we have come to know it represents the very antithesis of that which antedates hyperthyroidism in the white. All that we have been able to ascertain informs us that in the development of this disease in the negro other circumstances play a part more important than personality characteristics.

The apparentness of the disease, whereby the sufferer presents her disability to the sight of all is a factor. While due to its passivity it may lack the drama of a major hysterical convulsion, its appeal is undeniable and more dramatic than most that we know of in the world of sickness. All that happens to such sufferers is well known to our negro companions. The benefits to the white women in curtailing their sufferings and dangers in child bearing have, we are certain, been estimated with accuracy by their negro

contemporaries. The rapidity with which imitation has progressed in this regard among negroes has exceeded that noticed in other complexes such as gastric and duodenal ulcer because the picture has been necessarily more easily understood. We have every reason to believe that the development of Graves' disease in the negro race will become more frequent as time goes on, as they are educated by their own powers of observation as to how this condition can mitigate the harshness of their lives.

Case History and Postmortem. CASE 97577, C.P. About 6 weeks prior to admission she first notices a throbbing parietal headache. These headaches occurred 2 or 3 times daily and lasted over 30 minutes. Definite enlargement was noticed in the anterior part of the neck 1 month before she was admitted. Dyspnea came on 2 weeks before she was seen. This symptom with its accompanying nervousness was noticed after exercise and the taking of food. Associated with the shortness of breath was a distressing pain in the left anterior chest. Her estimation of her own weight loss was 35 pounds in the previous 6 months. She had had no previous operations. The family history was negative.

Physical examination showed a fairly well nourished negro woman of 38 years. The examination of the head and neck was negative with the exception of a smooth, bilateral enlargement of the thyroid gland. The chest showed a slight precordial pulsation and some evidence of cardiac enlargement. The heart rate was rapid, the rhythm good. A systolic murmur was present. The blood pressure was 146/70. The abdomen and pelvis failed to reveal any disorders. Tremor was marked. Fluoroscopic examination showed a substernal mass in the upper mediastinum somewhat more marked on the right side. The BMR was +37. Laboratory examinations were negative. Lugol's solution, sedatives and bed rest were employed for 8 days when the resulting improvement made surgical interference advisable.

Under cyclopropane anesthesia a subtotal thyroidectomy was done. The microscopic diagnosis was "simple parenchymatous hyperplasia of the thyroid gland." Postoperative improvement lasted less than 24 hours, to be terminated by the patient entering a thyroid crisis accompanied by high temperature, rapid pulse and uncontrollable nervous symptoms. Despite the use of oxygen, morphine in large doses and other appropriate measures the end came 3 days after the operation.

Autopsy Internal Examination. Gross. Head—not opened. Thorax—both lower lobes of the lungs were dark red, solid, heavy and a little wet. They sank promptly in water. The heart and great vessels were normal. The *thymus gland* was present and much enlarged—weight 85 gm. There was about four times the normal amount of fluid in the pericardial cavity.

Microscopic. The air sacs in the lower lobes of the lungs are pretty well filled with leukocytes, phagocytes and desquamated epithelial cells; also there is considerable coagulated non-cellular material. The heart muscle and coronaries and aorta were normal. The thymus gland was normal microscopically.

Diagnosis. Marked bilateral hypostatic, catarrhal pneumonia. Moderate fatty degeneration of the liver. Moderate passive hyperemia of the mucosa and submucosa of the stomach. Much enlarged and persistent thymus. Marked serous pericardial effusion.

This is the only instance of true thyroid crisis either postoperative or preoperative that we have observed in the negro patient. There have been occurrences of this complication in the white group. In

regard to the enlarged thymus gland found at postmortem it is interesting to recall that at Mount Sinai Hospital in New York, Moschcowitz[3a] reports that this condition was found in 95% of all fatal cases of Graves' syndrome. He quotes Seelig[4] and Haberer[1] to the same effect. The size of the organ is known, however, to be affected by the length of time that exists between death and the onset of disease.

Conclusions. 1. A short series of thyroid involvements occurring in the southern negro has been described.

2. From a comparison of whites living in the same locality and at a similar time period, the disease appears to be of approximately the same frequency in the two races.

3. Why this malady should develop with such frequency in the negro, when other sicknesses believed to be of a similar origin are rare, is unknown to us.

4. We think that its accessibility to inspection, the way in which it becomes one of the easily discovered and remembered portions of the personalities which it inflicts with its presence, are factors which cannot be disregarded.

5. The observations of McCarrison[2] as to its increased frequency among the native population of India after the return of native soldiers from the World War points toward the potency of imitation.

6. We have never been able to lose sight of the fact that the development of this sickness offers to women a means of escape from what they esteem to be other and more pressing dangers and discomforts.

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PSYCHIATRIC CONSULTATION SERVICE IN A MEDICAL IN-PATIENT DEPARTMENT. ITS FUNCTION IN DIAGNOSIS, TREATMENT AND TEACHING.

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In recent years the scientific study of the interrelationship between emotional factors and bodily processes has come to occupy an increasingly prominent place in medicine. Although the importance of the rôle that personality disorder may play in physical disease has been emphasized by psychiatrists[3] and internists for years, many physicians continue to think of an illness as being either mental or physical. The untenability of this concept of duality between

mind and body becomes clear when attention is paid to the study of individual patients through the coöperative efforts of the internist and the psychiatrist.

Consideration of the patient as a whole tends to be lost sight of in a large urban hospital. In such a setting it has become necessary for us to investigate much that the family physician knew through social contact in the community and visits to the homes of the people whom he treated. The understanding of patients, with emphasis on relieving their pains and allaying their fears, was taught to the young assistant or medical student who served as his apprentice.

The organization of the psychiatric consultation activities in the medical in-patient service of the New York Hospital illustrates a plan which has proved practical both for the study, diagnosis and treatment of the patient and for the teaching of the house staff of the Department of Medicine and the medical student.

One full-time physician has been assigned by the Department of Psychiatry to examine and treat patients with psychiatric problems on the medical pavilions. Consultations are at the request of the physician in charge. After the psychiatrist's initial interview the patient's illness is discussed with the internist who is encouraged to carry out psychiatric treatment if this is feasible. Many patients need more detailed investigation of the physical and emotional factors, which requires further discussion between the psychiatrist and the internist. Some cases are treated by the psychiatrist on the medical service. The psychiatrist spends one afternoon a week in the Psychiatric Out-Patient Department where psychotherapy which had been started on the medical service is continued with selected patients. Other patients who need further evaluation or treatment are seen in conjunction with the internist in the medical follow-up clinic. This clinic is designed to give the medical resident staff an opportunity to study the progress of patients who have been discharged from the in-patient service.

Many patients have presented diagnostic problems to the outside physicians who have referred them to the hospital for opinion. In this group are a large number whose illness is largely a psychiatric problem. It has been found that the patient welcomes an investigation of his personality reactions and situational problems as a part of a thorough study of his condition and that he looks upon it in much the same way as he does special examinations by other consultants.

Since the opening of the present building of the New York Hospital in 1932, from 127 to 164 patients on the medical pavilions have been seen annually by a psychiatric consultant. At first, the psychiatrist usually saw the patient once and gave a single written opinion. In the last 2 years, during which time the author has acted as psychiatric consultant, the work has been expanded so as to emphasize follow-up interviews for the purpose of either further contrib-

uting to the diagnostic formulation or carrying out psychotherapeutic procedures which may be indicated. During the past year, on a medical service of 111 beds, 218 patients out of 1409 admissions (15%) have been seen by the psychiatrist. In addition there were 443 follow-up interviews, making a total of 661 visits. The consultations on the four divisions of the service were as follows: male general medical pavilion, 91 out of 425 admissions (21%); female general medical pavilion, 79 out of 391 admissions (20%); chronic infectious pavilion, 26 out of 258 admissions (10%); acute infectious pavilion, 22 out of 335 admissions (7%).

Post-Graduate Teaching. The purpose of the teaching is to train the interns and residents to recognize psychiatric problems, to treat those of a simple type and to delegate treatment of the more complicated cases to the psychiatrist. Stress is laid on understanding the patient as a whole and the integration of the emotional and physical features of an illness. The knowledge of psychiatry which the house officer has obtained as a medical student can be reinforced and extended by its use in dealing with patients under his care.

Instruction is carried on by means of written reports and informal discussions with attention to the psychiatric principles involved. Contact with the diagnostic problems showing prominent psychiatric features which have not been recognized by others serves as a stimulus to the development of interest and awareness of problems which will require attention, no matter what the field of specialization may be. In the setting of a medical pavilion the practical value of psychiatry and its fusion into general medical practice can be clearly seen. Teaching of this type may well supply the need which has been recognized for post-graduate psychiatric teaching. In some hospitals this has been carried out by having the intern rotate through a psychiatric service or spend a period of time in a psychiatric hospital. If there has been satisfactory instruction in the psychoses in the medical school course in psychiatry, it may be more worth while to lay emphasis on the less severe psychiatric problems seen in the general hospital and to stress the application of psychobiological principles with attention to the hereditary, constitutional, economic, social and personality features as well as the purely medical aspects. The trained psychiatrist may thus be of value in contributing to the further understanding of emotional reactions of a type that the general physician will frequently see.

Teaching of Medical Students. With the expansion of the teaching of psychiatry in medical schools new emphasis has been placed on instruction by use of case material found in the general hospital.[1a]

Teaching of the third-year students in the Cornell University Medical College is carried on through presentation of patients both on the psychiatric in-patient service and the medical in-patient service, during the trimester they are studying psychiatry. Students are divided into groups of 6. Each group sees 9 patients on the

medical service. The patient is examined by the psychiatrist before the group, important facts of the history, and physical and laboratory findings are given, and the illness is discussed with special attention to the psychodynamics and the treatment. Each student is requested to write a report on 1 patient he has seen showing psychosomatic features.

During the trimester when the students are acting as clinical clerks on the medical service, 12 weekly conferences are held at each of which a student presents a case he has worked up. He is encouraged to develop an understanding of the factors which are important in the origin of the illness, both mental and physical, and their interrelationships in the patient he has examined and with whom he has had an opportunity to develop a doctor-patient relationship. After the student has presented his findings at the conference, the psychiatrist examines the patient before the group and demonstrates significant findings in the psychiatric examination and methods of psychotherapy. The last part of the hour is devoted to an open discussion which offers the whole group an opportunity to raise questions. Informal discussions with individual clinical clerks are also held.

Types of Problems. The psychiatrist is consulted about a wide variety of emotional reactions which range from mild incidental personality features to major psychotic developments. Billings has reported in a study[1b] of 745 cases examined that the general hospital offers an excellent cross-section of psychiatric material. The patients in our study may be divided into six groups for the purpose of discussion. An analysis has been made of 218 patients seen during a single year.

The first group consists of 26 patients (12%) with minor problems of personality adjustment in which the physician feels that the opinion and advice of the psychiatrist may be of value from the mental hygiene standpoint. In the analysis of the personality features of such patients the outline devised by Diethelm[2] has proven useful.

This type of problem is illustrated by the case of a 14-year-old school girl who showed signs of mild emotional instability and had difficulty in coöperating with the nurses while being treated for bronchopneumonia. The patient discussed her home and school difficulties which centered around the father's having divorced the mentally ill mother, the remarriage of the father, problems in her adjustment to both the mother and the stepmother, the antagonism of an older brother, and the change from a school where there had been considerable freedom to one which had a strict set of rules. After discussions with the psychiatrist the patient showed less emotional instability. In order to help the stepmother to understand the patient, a brief formulation of the patient's situation was presented to her.

In the second group of 62 patients (28%) are primarily psychoneurotic reactions which require a study of the development of the physical and emotional symptoms and their interrelationships.

A 34-year-old, married salesman presented the chief complaints of pins and needles sensations over the left side, headache, throbbing in the neck, "irritation of the left eyeball," hot sensations over the left ear, "paralysis of the intestines," generalized "numbness," and mild depressed feelings. No constant neurologic abnormalities could be demonstrated. During the interview with the psychiatrist the patient talked of minor worries and symptoms. He then became very tense and said that what had been bothering him was the fact that 3 months before admission he had been told by a physician that he had syphilis. Symptoms had developed rapidly after that. When he was assured that no signs of syphilis had been found and that his complaints could occur because of worry he was greatly relieved and had a dramatic disappearance of all his symptoms with restoration of confidence and a normal mood reaction.

A psychoneurotic reaction of longer duration is illustrated by the following case:

A 34-year-old, single, electrical engineer had complained of fatigue and poor health since the age of 15, which had become increasingly more marked so that he had done no work for 4 years. He insisted that he had some physical illness which no doctor had been able to discover. He was told that an investigation of his personality might be of help in understanding his illness. Many emotional problems centering around his sexual drive and dissatisfaction with his work were apparent. The relationship between emotional difficulties and the increased severity of his symptoms was seen by the patient. He accepted the formulation that his illness was primarily functional and after discharge continued to have psychotherapy in the Psychiatric Out-Patient Department, with marked improvement as shown by disappearance of excessive fatigue and ability to return to work.

In a third group are 71 patients (32%) with physical illnesses complicated by psychoneurotic features. The influence of psychogenic factors is frequently prominent in such conditions as hyperthyroidism, migraine, peptic ulcer, hypertension, and asthma. Combined treatment by the internist and psychiatrist is indicated.

A 50-year-old accident prevention inspector was admitted because of persistent hiccoughing which had prevented him from taking sufficient nourishment for 6 days. Previous studies indicated that he had spasms involving the gastro-intestinal tract in reaction to emotional difficulties of many years' duration. The hiccoughs disappeared under hypnosis, enabling the internist to proceed with a further investigation of his physical condition. Roentgen-ray examination revealed a diaphragmatic hernia which it was likely he had had for many years. The surgical consultant felt that operation was not indicated. It appeared that under increased stress caused by domestic quarrels and anxiety over his work the combined influence of the emotional factors and the physical abnormality resulted in the development of the hiccoughing.

A 30-year-old milk delivery man presented symptoms of Graves' disease. He had been well adjusted until after marriage to an unstable woman who had a psychoneurotic reaction of the anxiety type. He felt insecure in his work and wished to obtain a permanent position on a police force so that he would have the assurance of a pension. While on the waiting list for

this work he developed a duodenal ulcer. This lesion responded to treatment in the hospital. On returning to work he had more difficulty in making collections from his customers and had to work overtime. Over a period of eight months he had increasing symptoms of hyperthyroidism. He was relieved by unburdening himself, developed a calmer attitude toward his life situation, responded well to the treatment preparatory to operation, and made a good adjustment to his work after thyroidectomy.

A 15-year-old high school student had had recurrent asthmatic attacks for 1 year. When seen she had had four previous admissions to the hospital in the preceding month with prompt relief of symptoms as soon as she entered the hospital. Preceding her fifth admission she was brought to the accident pavilion appearing prostrated and moaning and groaning continuously. She told the psychiatrist that she was very sensitive about her height, that she was disturbed by breaking off a friendship with a boy, and that she had considered killing herself. Asthmatic attacks had been preceded on each occasion by considerable emotional tension. After discussions she developed understanding of her illness and felt more at ease. On discharge she was referred to the Psychiatric Out-Patient Department where in further interviews she emphasized that she was excessively dependent on her mother and that she had conflict over the possible effects of masturbation and what her behavior should be while out with boys. During the year following discharge from the hospital she had several very mild spells of wheezing when situational difficulties arose but no further severe attacks of asthma.

It is important to bear in mind that, although emotional problems may be in evidence, a concomitant physical illness is the most important aspect to be considered. In many cases mild emotional disorders occur in reaction to organic change. This type of reaction is illustrated by the case of a 28-year-old married physician who was admitted complaining of excessive fatigue and muscular weakness. Previous to admission several physicians had made a diagnosis of hysteria. When seen by the psychiatrist it was evident that the patient had become depressed secondary to his physical symptoms on realization that he had a serious neurological disease—myasthenia gravis. There was marked improvement upon the administration of prostigmine. During discussions emphasis was laid on encouraging him to continue to lead as active a life as was compatible with his physical disability.

In a fourth group of 30 patients (15%) are those with findings on psychiatric examination indicating cerebral organic changes which were not severe enough to be diagnosed as a psychosis. Early changes due to arteriosclerosis, syphilis, alcohol, and pernicious anemia are included.

All patients with syphilis of the central nervous system have psychiatric examinations before and after malarial therapy in order to give diagnostic help and to aid in establishing the degree of improvement after treatment. Of the 17 patients examined, 13 showed some evidence of organic cerebral involvement. The value of psychiatric examination is illustrated by the following case:

A 45-year-old married man, 20 months before had been treated with malaria because of physical and serologic findings characteristic of general

paresis. Although he made a good superficial appearance and had no subjective complaints it was noted on detailed psychiatric examination that he showed definite memory changes, inappropriate emotional responses, a false sense of well being, and poor judgment. It was evident that organic cerebral changes on the basis of general paresis were progressing and that another course of malarial therapy was indicated.

In a fifth group are 20 patients (9%) with psychotic reactions, both functional and organic, including schizophrenia, manic-depressive psychosis, general paresis, delirium, arteriosclerotic and senile reactions, epileptic psychosis, brain tumors, and feeblemindedness. Frequently the psychiatrist can make suggestions which may be helpful in managing such patients on the medical service. If treatment cannot be continued in the general hospital, advice may be given about arrangements for transfer to a psychiatric hospital.

A 30-year-old married automobile washer was admitted with lobar pneumonia. He developed a delirium which made it difficult to give him proper care because of his uncoöperativeness. He showed marked resentment to the fact that so many people were caring for him and made reference to suicide. Arrangements were made to have only two nurses care for him, which seemed to relieve him to a great degree. He responded some to reassurance even at times when he expressed many suspicions. When his delirium had cleared it was apparent that he had been psychoneurotic for many years. After discharge treatment of his emotional difficulties was continued in the medical follow-up clinic.

The following case illustrates the type of reaction that may require transfer to a psychiatric hospital.

A 45-year-old housewife who was going through the menopause complained of multiple physical complaints and of feeling depressed. Careful investigation failed to reveal any evidence of physical disease. Physical complaints continued. Further study showed that she was developing somatic delusions. A diagnosis of depression in the setting of the menopause was made. Since she did not improve, transfer to a psychiatric hospital became necessary.

In the sixth group are 9 patients (4%) who on psychiatric examination had no findings which could either add appreciably to the understanding of the patient or contribute positive findings to the formulation of his illness. The following case demonstrates the need for sufficient evidence in order to make a diagnosis of psychoneurosis and the significance of negative psychiatric findings.

The patient was a 45-year-old porter who complained of pain over the lower half of the back and the entire abdomen of increasing severity for two months. Studies of his physical condition failed to reveal any lesions except for an abnormal glucose tolerance curve showing consistently high blood sugar values. On psychiatric examination he showed no evidence of personality maladjustment and gave no history of emotional disturbance which might account for the development of his symptoms. He continued to have more pain, developed palpable abdominal masses, rapidly became weaker and died 3 months after being seen by the psychiatrist. The postmortem examination showed carcinoma of the pancreas with extensive metastases.

Summary. The organization of the activities of a psychiatric consultation service in a medical in-patient department as described illustrates a plan which has proved to be practical. It has been found that a large percentage of the patients admitted presented problems in which coöperative investigation by the internist and psychiatrist was of definite value in diagnosis and treatment. An analysis of 218 patients, who represent 15% of the admissions during a single year to the medical pavilions, shows that 12% may be classified as having minor, incidental personality problems, 28% psychoneurotic reactions, 32% physical illness complicated by psychoneurotic features, 15% mild organic cerebral changes and 9% psychosis. In 4% there were no positive psychiatric findings which contributed to the diagnostic formulation.

Post-graduate and undergraduate teaching was carried out by individual discussions and group conferences. Stress was placed on obtaining a better understanding of the patient as a whole by considering the individual personality and its relations to somatic functions.

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THE INITIAL NERVOUS SYNDROME OF PELLAGRA AND ASSOCIATED DEFICIENCY DISEASES*

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It has been known for many years that pellagrins in relapse often manifest psychotic changes.[6,9] The association of so-called psychoneurotic symptoms with subclinical and mild pellagra is recognized less frequently and many patients with such symptoms are diagnosed as "neurasthenics."[7,8] Evidence accumulated from the study of over a thousand pellagrins during the past 10 years convinces

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that these symptoms have certain distinctive characteristics and that they are of significance in making an early diagnosis of the disease. Although it has been known that these symptoms improve dramatically following nicotinic acid therapy, a satisfactory study of the characteristics has not been reported since the initiation of this therapy. The present communication reports a specific study of the initial nervous symptoms in subclinical and mild pellagrins.

Sixty cases of pellagra (many of which had an associated beriberi and riboflavin deficiency) were selected for this investigation, which is restricted to an analysis of the symptoms and experiences reported by the patients. The psychiatric information obtained was gathered during repeated interviews lasting from 1 to 2 hours and by therapeutic tests in which suggestion was eliminated. Neurological studies, which will be reported separately,[5] were made on a number of these patients. The symptoms thus observed objectively are not all included in this report, but in certain instances are correlated with it.

The so-called psychoneurotic syndromes usually draw their contents from the life of the individual, particularly from the experiences and traumas of childhood and youth. Consequently, the basis of the neurosis may vary greatly from one person to another. We soon learned that among the pellagrins included in the present study, there was an amazing uniformity of mental symptoms which varied in intensity and had no connection with the single personality.* These common symptoms had elementary features and followed the same pattern. They may be classified as follows:

A. The Elementary Syndrome:
   1. Psycho-sensory disturbances.
   2. Psycho-motor disturbances.
   3. Emotional disturbances.

B. General Symptoms of the Central Nervous System:
   1. Weakness and increased fatigability.
   2. Sleeplessness.
   3. Headaches.

The first group of symptoms resembles those which may be found in disease of the basal ganglia and thalamus, while the second group represents general symptoms which usually accompany any disturbance of the central nervous system. The subsequent description demonstrates that both sleeplessness and headaches of pellagrins exhibit some special features which are uncommon and therefore are useful in making a differential diagnosis.

* Examination of the heredity factors of 32 patients revealed: left-handedness in 19 of their families; migrainous headaches in 16 families; convulsions (different types) in 9 families; stuttering in 8 families; feeblemindedness in 4 families; and other mental heredities in 2 families. The patients in this series were prone to have more than one of these stigmata; for instance, migrainous headaches occurred 12 times in combination with left-handedness, convulsions, stuttering or feeblemindedness; convulsions of different types occurred 8 times, and stuttering 5 times with one of the other factors. In this small group of patients epileptoid heredity prevailed. However, the significance of this finding requires a special investigation.

A. The Elementary Syndrome. 1. *Psycho-sensory Disturbances.* Psycho-sensory disturbances occur in all special senses. Patients describe all outward perceptual impressions as making them feel "uneasy," or as "bothering" or "hurting" them. They dislike bright light and bright colors, and sometimes state that bright colors "run together." Noises are even more annoying than light, and sudden noises, such as the slamming of a door or the scream of a child, produce immediately an emotional shock and make the patient feel "jerky and shaky." Music of any kind makes them "uncomfortable," and many who enjoyed radio music when in good health are now forced to forego this pleasure. In the more severe cases, continual noises are almost "unbearable." Patients who paid no attention to odors prior to their illness now find odors, particularly those of the kitchen and factory, so disagreeable that they sometimes cause nausea and vomiting. Several patients stated that cooking has become "an agony." Certain strong odors, such as those of lysol, ether, or garbage, formerly considered merely unpleasant, now actually cause distress. Taste has changed to such an extent that foods formerly preferred are now disliked intensely. No rule can be established in regard to change in taste; highly seasoned food have become disagreeable to most patients, sweet foods to some, fried meats to others, and still other patients complain that some particular vegetable causes nausea. The patients can be characterized as being "on edge," irritable and tense.

Many abnormal sensations of the skin were noted. No definite differentiation could be made between those which have been considered to be subjective and those which might be caused by associated peripheral neuritis.

A prominent complaint should be stressed: patients complain of dizziness, particularly after sudden movements. Getting up, turning the head, and bending forward, immediately produce a feeling of uncertainty and difficulty in keeping balance. Patients usually have the impression of being whirled around their vertical axis, although occasionally they feel as if things are whirling around them. Simultaneously, flickering stars and dark spots appear in the direct field of vision. Sometimes the direct fixation of the eyes on an object and a strenuous stare stop the dizzy sensation. Many patients complain of dizziness while standing still and watching traffic. The majority of patients state that their weakness and dizziness is immediately increased in heavy traffic.

2. *Psycho-motor Disturbances.* In these patients the motor drive is increased. Occasionally, the attitude of the patient is quiet and they state that they are restless only on the "inside." But as a rule, they are fidgety, change their position frequently, and move around a great deal. The degree of restlessness is slight if compared with the restlessness of an apprehensive melancholic or with the excite-

ment of a severe anxiety state. Patients complain that they feel tense and have a desire to quarrel. Sometimes after quarreling their tenseness is relieved, but more frequently it is increased. They all complain that a sudden noise or a flash of light makes them jump and twitch, indicating an increased preparedness for motor action.

3. *Emotional Changes.* Emotional reactions are increased. Patients are more excitable and more sensitive than they were before their illness. Moreover, the emotional reactions are directed toward a depressive response, and a sad and gloomy mood prevails. The most striking feature of emotional feature is constant apprehension. It is not exhibited in such a demonstrative manner as in the usual neurotics, and it rarely reaches the intensity of melancholic apprehensive agitation. Many of the patients express various fears, frights and phobias, although they make a conscious attempt to suppress them. Nevertheless, this constant apprehensive mood often changes the habitual attitude of the patient. For example, a brawny coal miner said, "I'm scared to death. If I see two men fighting with their fists, it seems to me that I will pass out." Before he became ill he used to look for quarrels and liked to engage in prize fights. The emotional outlook toward the future is gloomy and pessimistic, and imminent danger is expected constantly. If patients are asked what they think when they see two cars passing each other, they invariably reply: "I expect a crash."

It is remarkable that these patients make little or no attempt to explain and to rationalize all these strange experiences. In the process of the development of psychoneurosis, somatic sensations may be compared to tools which the personality uses in order to strengthen its defenses against latent conflicts. Many neurotics are unhappy and desperate about their own unhappiness. This attitude is not characteristic of pellagrins. They describe symptoms that are strange to themselves, self-distant, and not connected with their personal life. To them these symptoms are just as elementary as aches and pains in the extremities, burning of the skin, or sensations caused by changes in the alimentary tract.

B. General Symptoms of the Central Nervous System. 1. *Weakness and Increased Fatigability.* Although increased motor drive and restlessness are apparent, these patients complain of weakness. This may be due to neuritic changes and an insufficient caloric intake. However, the degree of weakness does not parallel the changes observed by Lewy, Spies and Aring[8] in chronaximetric examinations, and many persons whose caloric intake was adequate complained of weakness. Weakness, observed objectively, may not reach a high degree; patients are often able to do much of their work, yet they tire easily. There is a constant struggle between restlessness and the desire to rest, with restlessness often prevailing.

2. *Sleeplessness.* In many cases, sleeplessness is a major symptom. Patients usually fall asleep between 12:00 and 2:00 o'clock at night and awaken at about 5:00 in the morning. Frequently, even this short period of sleep is interrupted. Patients state emphatically that their sensory disturbances do not prevent them from falling asleep or cause them to awaken, thus further differentiating this nervous syndrome from the usual one of psychoneurosis. In spite of the constant apprehensive attitude, no bad dreams or nightmares were reported.

3. *Headaches.* Many patients report having had "sick headaches" since childhood. The headaches prior to the onset of pellagra and the headaches associated with pellagra resemble migrainous syndromes in many features. The headache usually seen in these cases occurs suddenly. It is localized in the forehead and in the temples, and is accompanied by scintillating scotomas. Nausea and vomiting are reported frequently, and sometimes relief is felt after vomiting. Many patients have dizzy spells along with the headaches. The headache syndrome exhibited by these patients is clinically indistinguishable from migraine.

Although this nervous syndrome has been found regularly in these cases of developing nutritional disturbances, the question arises as to whether these changes are produced directly by a specific deficiency of a single chemical substance. To determine the effect of certain of these nutritional substances, a few crucial studies were made. Pellagrins were given large amounts of either cocarboxylase, nicotinic acid, riboflavin, or synthetic vitamin B_1. Neurologic and nervous changes were studied, and certain metabolic determinations were made on samples of blood before and after therapy. The correlated results will be published in another paper. It may be noted, however, that the intravenous injection of cocarboxylase or vitamin B_1 produced an immediate reversal of the neurologic signs within a few hours, while nicotinic acid, administered orally, produced a similar effect after a longer period of time. In contrast, the oral administration of riboflavin had no such effect upon the symptoms arising from the nervous system.

The following case report illustrates the effect of cocarboxylase therapy:

June 22, 1939. Mrs. F. F., a white pellagrin of 39 years complained of ill-health during the spring and summer of the past 3 years. She said that her mouth became sore, that her stomach felt "sick," and that her back and arms ached. Noises made her "jumpy and shaky," and odors "bothered" her. Sudden movements caused dizziness. She was restless, excitable, and easily frightened. She felt depressed and was apprehensive, constantly expecting some harm to befall her family. She tired easily; but although she felt tired, she kept busy all day because she was too "fidgety" to rest. She seldom fell asleep before 2:00 A.M. and usually got up at 5:30 A.M.

A total of 200 mg. of cocarboxylase* was administered intravenously in 50 mg. doses within a period of 2 hours. One hour later she reported that she felt relaxed and stronger, that she had ceased to worry, and that she felt like resting. That night she fell asleep at 9:00 P.M. and awoke at 5:30 A.M., feeling rested. She stated that her nerves were "a whole lot better" and that she had not "felt so well in three years."

Following the administration of cocarboxylase the bisulphite-binding substances in the blood decreased. Neurologic examination showed that the severely disturbed touch and pain sensitivity which had been previously found, returned to normal within 24 hours. The corneal reflex, which had almost disappeared, improved significantly. Pupillary motor reaction and differentiation of brightness, though normal throughout this study, increased in acuteness for a period after the injections. However, abnormal tendon reflexes, nystagmus, and weakness of convergence remained unchanged after the medication.

Either cocarboxylase (or vitamin B_1) or nicotinic acid may relieve the initial nervous symptoms of a developing nutritional deficiency; and both of these substances have been found to be involved in the process of oxidation of carbohydrates.[2] Lack of either may cause changes in the brain which, in turn, alter carbohydrate metabolism. The investigations of Himwich and Nahum[3] and Lennox[4] have shown that the brain utilizes predominantly carbohydrates. Any change in the metabolism of carbohydrates may influence the functions of the brain. In experiments on excised tissues, Dixon and Meyer[1] showed that the cerebral cortex and the cerebellum have the highest metabolic requirements of the brain structures. Hence, these parts should be the first to be affected by metabolic changes.

Discussion. It has been emphasized that no connection could be established between the experiences of the single personality and the initial nervous syndrome of pellagra. The complaints of these patients were practically identical, regardless of whether their personality was simple or complicated, or whether they were illiterate or educated. Clinical observation revealed no causal relationship of the symptoms to environmental stresses and strains, to personal conflicts, or to any of the other usual underlying causative factors of neurosis. It appears, therefore, that this nervous syndrome may indicate a disturbance of the central nervous system. Large doses of vitamin B_1 or nicotinic acid relieved the symptoms rapidly.

The symptoms of the initial psychiatric syndrome of pellagra are definite. They are especially important to the physician treating the subclinical cases in which the signs of pellagra are inconclusive. Since nutritional deficiencies may be related to neurotic

* Furnished through the courtesy of Merck & Co., Rahway, N. J.

manifestations, examination for the nervous symptoms of such deficiencies should become a matter of routine psychiatric examination. Administration of large amounts of either nicotinic acid or thiamin, under controlled conditions, will aid in establishing the correctness of the diagnosis.

Attention may be called to another important aspect of the problem. It has been shown by this study that developing pellagra often causes a rapid breakdown of personality. Men previously strong, courageous, and enduring, become shaky, weary, and apprehensive even before the usually recognized clinical signs of pellagra develop. Nutritional deficiencies widespread in a population may not only weaken the strength, but may also break down the morale. Subclinical pellagra or beriberi may be an important factor in the fighting morale of an army, supporting Napoleon's contention that "an army marches on its stomach."

Conclusions. 1. Sixty patients with subclinical and mild pellagra and associated deficiencies were examined and special attention given to their subjective symptoms. The symptoms were found to be uniform, and they had no connection with the personality.

2. The symptoms of the initial nervous syndrome associated with pellagra are: *a*, hyperesthesia to all forms of sensation; *b*, increased psycho-motor drive; *c*, increased emotional drive with a definite trend toward depression and apprehension; *d*, weariness and increased fatigability; *e*, headaches; and *f*, sleeplessness. In general, these patients appear to have anxiety states with depressive features.

3. The etiology of this syndrome was established by the administration, under controlled conditions, of large amounts of nicotinic acid, cocarboxylase, or vitamin B_1. Following the administration of these substances, the symptoms diminished rapidly in intensity or disappeared entirely. Despite the clear-cut manner in which these substances are specific, the usual case, in addition, should have a well-balanced diet. Riboflavin and vitamin B_6, however, did not produce the same effect.

4. Nutritional deficiencies may be involved etiologically in psychiatric disturbances.

5. This investigation indicates that nutritional deficiencies may cause a disintegration of the personality, including a breakdown of morale.

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THE ABSENCE OF REACTIONS FOLLOWING THERAPEUTIC DOSES OF NICOTINIC ACID AMIDE.

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Nicotinic acid, first used by Elvehjem, Madden, Strong and Wooley[4] to cure black tongue or canine pellagra, has been amply demonstrated to have remarkable curative value in human pellagra.[5,9,13] This is so, despite the fact that pellagra is a syndrome due to multiple deficiencies and that patients who are deficient in one factor of the vitamin B complex may be expected to be deficient in and need supplements of other factors to produce a complete cure.[6,10,11,15]

Free nicotinic acid has not been found in animal tissues. It is not the complete vitamin. Elvehjem and his associates[4] isolated nicotinic acid amide from liver extract. Nicotinic acid is a necessary building stone with which the organism can synthesize complex molecular structures, which act as enzymes, essential for normal cellular metabolism.[3,17] Consequently, it is not surprising that nicotinic acid should have pharmacological effects of its own, if it is absorbed more rapidly than the organisms can synthesize it into the natural vitamin. These effects have been reported by others.[8,12,14] Unless large doses of nicotinic acid are given, unpleasant symptoms are limited to a peripheral vasodilatation with increase in skin temperature and sensations of burning, itching or tingling which is usually most pronounced in the face and ears. This need not be serious, because it does not usually occur after moderate doses until the patient has received nearly the therapeutic amount of the drug.

Nicotinic acid amide has been reported by several workers to be effective in the treatment of human pellagra.[1,2,7,13] Because nicotinic acid amide is a substance occurring naturally in the body, it seemed likely that it would not produce reactions like those produced by nicotinic acid. Vilter, Bean and Spies[16] reported that the intravenous injection of "much larger" doses of nicotinic acid amide did not produce flushing reactions. Alport, Ghalioungui and Hama[1] reported that 1 gm. doses of nicotinic acid amide led only to transient headache in 2 cases; it was not stated when in the course of treatment these large doses were given.

Our experience confirms that of Spies, Bean and Stone[12] and others that reactions to nicotinic acid are less frequent and less intense in pellagrins than in normal individuals. Among a large number of patients treated, most of whom would be classed as chronic or "subclinical" pellagra, we have seen only 4 who had mild flushing

following one of the early 60 mg. doses and these reactions did not recur consistently until after a good number of further doses. Consequently it seemed desirable to test further the tolerance for nicotinic acid amide.

Method. Seventeen patients were given nicotinic acid until they consistently had flushing reactions following 40 mg. doses, given in tablets by mouth after meals. The first 5 patients were then given nicotinic acid amide in tablets by mouth, before meals.* The initial dose was 100 mg. Each subsequent dose was increased by 100 mg. until these patients took doses of 300, 300, 400, 500 and 500 mg., respectively. One patient took 1.2 gm. in 3 consecutive doses of 300, 400 and 500 mg. within 10 hours.

Skin temperature determinations were not made because the peripheral vasodilatation which is produced by nicotinic acid is readily apparent. No cutaneous flushing was observed in, and no abnormal cutaneous sensations were reported by, any of these patients. No abdominal or cerebral symptoms such as may follow large doses of nicotinic acid were reported. No significant change in pulse rate or blood pressure was observed. There was no change in the electrocardiograms of 2 subjects following the ingestion of 500 mg. of nicotinic acid amide. There was a slight decrease in amplitude of the *T* wave in Lead II in one subject who subsequently was given 750 mg. of the drug by mouth.

Such large doses would rarely be indicated. Consequently, in subsequent observations, 12 patients who had been saturated with nicotinic acid as described for the first subjects were given single doses of 250 mg. of nicotinic acid amide, by mouth, before meals. In no instance has there been any evidence of a toxic effect.

Summary. Doses of nicotinic acid amide up to 500 mg. by mouth, while fasting, have been given to patients who had previously been saturated with nicotinic acid so that they consistently had flushing reactions following 40 mg. doses, orally, after meals. Ingestion of these doses of the amide was not followed by peripheral vasodilatation or any other of the symptoms which follow the ingestion of large doses of nicotinic acid.

* Nicotinic acid was furnished by the Upjohn Company; nicotinic acid amide was furnished by General Biochemicals, Inc.

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BOOK REVIEWS AND NOTICES

PROCTOSCOPIC EXAMINATION AND DIAGNOSIS AND TREATMENT OF DIARRHEAS. By M. H. STREICHER, M.S., M.D., Assistant Professor of Medicine, University of Illinois, College of Medical Research and Educational Hospital, and Department of Surgery, Grant Hospital of Chicago. Pp. 149; 39 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $3.00.

THIS is a very simply written little book which discusses briefly the instruments that are used for proctoscopic and sigmoidoscopic examinations and the technique used in the passing of the instruments. The story is related so briefly that one gets the impression that there is really very little skill necessary in doing a good examination. Some very interesting illustrative cases are given in Chapter IV, but far too few for the neophyte to obtain more than a very superficial knowledge. Part II, which discusses the diarrheas, is also brief but well done. There is a satisfactory bibliography. The volume would be more widely read were the price not so high for the amount of material it contains. I. R.

RECENT ADVANCES IN MEDICAL SCIENCE. A Study of Their Social and Economic Implications. By SIR EDWARD MELLANBY, K.C.B., M.D., F.R.C.P., F.R.S., K.H.P., Secretary to the Medical Research Council. (The Rede Lecture delivered before the University of Cambridge on April 28, 1939.) Pp. 62. Cambridge: At the University Press; New York: The Macmillan Company, 1939. Price, 75c.

IN this small volume the author discusses the significance of medical science as related to society as a whole. It is enlightening, interesting and convincing. If we agree with him that human life and health, developed and enjoyed to a maximum degree by each individual, are themselves the most precious of all things in the world, then medical science may be regarded as the most concrete factor in advancing civilization. The author traces back to medical science some of the most desirable characteristics of modern society, such as cleanliness, but he also points out that there is an unreasonable lag in the time between the disclosing of new medical knowledge and its application for the benefit of society as a whole.

The relation of medical science to medical practice and to public health, the influence of medical science on health, fertility and population, and its necessary rôle in making tropical countries habitable for those who can do most in their development, are among the topics discussed in this lecture. It is distinctly encouraging to read a summary of the effects of the advances in medical science, and the possibilities that are indicated for the future are stimulating. The lecture closes with this statement: "There is no limit to the amount of knowledge to be gained, if the medical scientist is given the opportunities and facilities for his work. Would that the same could be said about the wisdom necessary to make the best use of this knowledge."

This brief résumé of the significance of medical science should be read by students of medicine, by those engaged in medical research and by anyone interested in general problems of health, as a means of orientating themselves more fully in the larger needs of modern society. G. R.

THE ELECTROCARDIOGRAM AND X-RAY CONFIGURATION OF THE HEART. By ARTHUR M. MASTER, B.S., M.D., F.A.C.P., Associate in Medicine, and Chief, Cardiographic Laboratory, the Mt. Sinai Hospital, New York; Associate in Medicine, The College of Physicians and Surgeons, Columbia University, New York. Pp. 222; 71 cases with 204 engravings. Philadelphia: Lea & Febiger, 1939. Price, $6.50.

THIS is a concise atlas emphasizing the correlation to be found between the size, shape and position of the heart and the electrocardiographic pattern. The numerous plates are clearly reproduced, with teleoroentgenograms and electrocardiograms placed adjacently. The legends and the bibliography are adequate. A few of the electrocardiographic patterns attributed to alterations in the electrical axis might also be interpreted as being due to myocardial damage. The book is to be recommended as a most useful source for reference, either for the beginner, or for one interested in enlarging his knowledge concerning the author's timely point of view.

W. J.

NITROUS OXIDE–OXYGEN ANESTHESIA. McKesson-Clement Viewpoint and Technique. By F. W. CLEMENT, M.D., Director of Anesthesia at Flower Hospital, The State Hospital for the Insane, Lucas County Hospital, Toledo Dental Dispensary; Anesthetist to Toledo, Mercy and St. Vincent Hospitals, Toledo, etc. Pp. 274; 70 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $4.00.

THE author has combined his ideas on nitrous oxide with those held by the late E. I. McKesson. General topics such as preoperative sedation, respiration, anoxemia, shock, and others are considered. The most extensive uses ever made of nitrous oxide are described in some detail, but the author has not reckoned with the limitations in skill of the average anesthetist with this anesthetic. The anesthetic techniques in common use with inhalation anesthesia, also special methods, are described in connection with nitrous oxide, cyclopropane and ether. The book is a contribution to anesthesia; however, it can only be recommended with some reservation in light of the recent knowledge of insidious damage from oxygen shortage to various body tissues. Anesthetists should find the book practically useful as well as a memorial to Dr. McKesson.

I. T.

HARVEY CUSHING'S SEVENTIETH BIRTHDAY PARTY, APRIL 8, 1939. Speeches, Letters, and Tributes. Pp. 146; 9 illustrations. Springfield, Ill.: Charles C Thomas, 1939, for The Harvey Cushing Society. Price, $3.00.

SIX months before Dr. Cushing's death almost to a day, the Harvey Cushing Society celebrated with him his seventieth birthday. In order to allow his many admirers who were not able to be present "to share with the Society and its guests a little of the warmth and gay intimacy of the occasion," this small volume of speeches, letters and tributes has been prepared. It is a welcome companion to the Cushing Bibliography.

E. K.

PHYSIOLOGICAL DIFFERENTIATION IN *Lymnæa Columella*. By JOSHUA L. BAILY, JR. With a Foreword by RAYMOND PEARL. (The American Journal of Hygiene, Monographic Series, No. 14, April, 1939.) Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 133; illustrated. Baltimore: The Johns Hopkins University Press, 1939. Price, $1.00.

THIS very adequate biometric treatment of painstaking series of observations proves that the offspring from two populations of a pond-snail, collected somewhat over 100 miles apart but raised under identical laboratory

conditions, showed very significant differences between statistical means, obtained from physiologic characteristics of longevity, fecundity and growth. One of the populations seemed to constitute a more settled and stable stock, with less acute infant mortality and less variability with respect to longevity and fecundity although not in regard to growth. However, the Reviewer suspects that equally accurate measurements of morphologic structures might disclose similar divergences between the means of the two stocks, even though inspection did give valid evidence of their close intergradation in shell-form. H. B.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. 11, Scarlet Fever to Testis, Undescended; Vol. 12, Tetanus to Yellow Fever. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.CH., M.S., F.R.C.S., JAMES YOUNG, M.D., F.R.C.S. ED., SIR LEONARD ROGERS, M.D., LL.D., F.R.C.P., and F. M. R. WALSHE, M.D., D.Sc., F.R.C.P. Pp. 730; 93 illustrations and 17 plates (6 in color) (Vol. 11); Pp. 726, 48 illustrations, 12 plates (3 in color) (Vol. 12). London: Butterworth & Co. (Publishers), Ltd., 1939. Price, $12.00 per volume.

AMONG the more important articles in Vol. 11 are those on Sex Hormones, Occupational Diseases, Skin Tumors, Spinal Cord Diseases, and Syphilis (this approaches monographic proportions).

More than one-fifth of Vol. 12 is devoted to the toxicology of criminal, accidental and industrial poisonings, and the subject is further augmented by many cross-references. This is a well-considered, useful up-to-date presentation of a subject none too well represented in English medical literature. Of the other longer articles, one notes that more space is given to typhus fever than to tuberculosis; more to yaws than to yellow fever. Disorders of the Uterus is given 78 pages; Tumours only 11. The 35 pages on Vitamins are useful. Though some of the latest developments, such those of vitamin K, are missed, the difficulty in keeping abreast with this rapidly moving subject is appreciated by the Reviewer. In fact, these volumes can be warmly recommended, for the reasons already given in notices of earlier volumes. E. K.

MALARIA IN PANAMA. (The American Journal of Hygiene, Monographic Series, No. 13, January, 1939.) Supported by the De Lamar Fund of The Johns Hopkins University. By JAMES STEVENS SIMMONS, B.S., M.D., PH.D., S.D., Lieutenant Colonel, Medical Corps, U. S. Army; President, Army Medical Research Board, Ancon, C. Z., 1934–5. With the Collaboration of GEORGE R. CALLENDER, M.D., Lieutenant Colonel, Medical Corps, U. S. Army, etc., DALFERES P. CURRY, M.D., Major, Medical Reserve Corps, U. S. Army, etc., SEYMOUR C. SCHWARTZ, B.S., M.D., DR.P.H., Lieutenant Colonel, Medical Corps, U. S. Army, etc., and RAYMOND RANDALL, D.V.M., Lieutenant Colonel, Veterinary Corps, U. S. Army, etc. Pp. 326; 32 figures and 58 tables. Baltimore: The Johns Hopkins Press, 1939. Price, $1.10.

IN spite of adequate understanding of the nature of malaria and well-developed control practices and clinical management, this disease still remains the great obstacle to development of tropical lands. The Canal Zone of Panama is one region in the tropics where neither funds nor personnel have been stinted in the effort to be rid of malaria. Yet certain problems are still to be solved. The authors of this account have done a valu-

able service in gathering and analyzing the great amount of material that is available. The book is divided into three sections: Part I, "Malaria on the Isthmus of Panama (1501–1938)" is made up of two chapters and notes on the history of malaria on the isthmus of Panama, and the present distribution of malaria in the Republic of Panama. Part II, "Malaria in the Panama Canal Zone (1904–1938)" contains five chapters in which are discussed the Canal Zone, malaria among Panama Canal employees, human carriers of malaria in the Canal Zone, the anopheline mosquitoes of the Canal Zone, and sanitary methods used for the control of malaria in the Canal Zone. Part III is an account of malaria in the military forces of the Canal Zone (1911–1938) separated into four chapters. A brief résumé, a bibliography and index complete the book. H. R.

SUPERFLUOUS HAIR AND ITS REMOVAL. By A. F. NIEMOELLER, A.B., M.A., B.S. With a Foreword by M. H. MARTON, M.D. Pp. 155; illustrated. New York: Harvest House, 1938. Price, $2.00.

IN this small volume the author summarizes briefly existing knowledge regarding a problem of considerable importance to the individual suffering from an unusual growth of hair. He discusses briefly the question of anatomy, the methods of hair removal employed in various parts of the world, and the various techniques that are used. This is followed by chapters dealing with the removal of hair as it is carried out in the various parts of the body by experts, and a final chapter deals with its removal by the patient herself. Numerous prescriptions for depilatories are included. The volume would seem to have a very definite value in the library of the dermatologist and cosmetician, but in the hands of the layman might easily lead to undesirable complications. D. M.

CARDIOVASCULAR DISEASES. Their Diagnosis and Treatment. By DAVID SCHERF, M.D., and LINN J. BOYD, M.D., F.A.C.P., Associate Professor of Clinical Medicine and Professor of Medicine, respectively, The New York Medical College, Flower and Fifth Avenue Hospitals. Pp. 458; 10 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, $6.25.

THIS is a very readable adaptation of Dr. Scherf's *Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen* (Vienna, Julius Springer, 1938). It contains well-indexed dissertations on all of the important aspects of cardiovascular disease. Emphasis is placed upon physical diagnosis, abnormal physiology, and principles of treatment. For the physician desiring to enlarge his knowledge in this field, the book will supply much of practical value. There are many concepts and recommendations of continental flavor, all of which the critical American reader will not be able to accept. W. J.

ARCHITECTURE OF THE KIDNEY IN CHRONIC BRIGHT'S DISEASE. By JEAN OLIVER, Professor of Pathology, Long Island College of Medicine; Pathologist, The Hoagland Laboratory; Formerly Professor of Pathology, Stanford University. Pp. 195; 59 text illustrations (some in colors); 23 plates; 16 stereograms. New York: Paul B. Hoeber, Inc., 1939. Price, $10.00.

THIS book is a significant contribution to studies in the pathology of Bright's disease, a tribute to painstaking research and a challenge to further investigation along these lines. The author's premise, that the necessity of basing a three-dimensional histopathologic concept on deduction from a two-dimensional picture may lead to grave error in the true visualization

of the diseased kidney, seems to be a logical one. By means of microdissection and plastic reconstruction techniques the author has studied a number of diseased kidneys, comparing his own morphologic findings with the flat histologic sections of the same tissues and the clinical course of the patient. These studies are copiously illustrated with drawings and photographs. The author also reëxamines various theories regarding the altered morphology of the diseased kidney in its relation to altered function and finds certain of them lacking in the light of his own investigations.

Certainly the morbid anatomic basis of Bright's disease is a shifting one. These investigations and further investigation with the three-dimensional concept as a background will do much to fix the pathologic basis firmly, which in turn will aid greatly in solving the vital problem of accurate correlation between the clinical manifestations and altered morphology in Bright's disease. F. M.

PROTOZOÖLOGY. By RICHARD ROKSABRO KUDO, D.Sc., Associate Professor of Zoölogy, The University of Illinois. Enlarged and completely rewritten edition of Handbook of Protozoölogy. Pp. 689; 291 illustrations. Second edition. Springfield, Ill.: Charles C Thomas, 1939. Price, $6.50.

IN preparing a second edition of his "Handbook of Protozoölogy," the author has not only revised, but has rewritten and greatly expanded the text, and has therefore given it a new title. There are many new and up-to-date illustrations and many of the former figures have been redrawn, regrouped and enlarged. Much new material has been added to the introductory section which now includes chapters with the headings: 1, Introduction, 2, Ecology, 3, Morphology, 4, Physiology, 5, Reproduction, 6, Variation and Heredity. A total of 170 pages is devoted to this series of chapters in contrast to the 59 pages of introductory material of the earlier edition.

The taxonomic part of the book, which covered 360 pages in the previous edition, has been expanded to 471 pages. The taxonomy has been modernized throughout, but more especially in the parts dealing with the Mastigophora, Sporozoa and Ciliata. In the new edition, 1075 genera and 1530 species are characterized in comparison with 686 genera and 915 species in the "Handbook." The appendix of the first edition has been omitted, but the index, which filled 30 pages in the earlier edition, has been expanded to 46 pages in the new. Altogether, this rewritten, enlarged and modernized "Protozoölogy" is a distinct advance over the earlier "Handbook of Protozoölogy" by the same author. D. W.

PERSPECTIVES IN BIOCHEMISTRY. Thirty-one Essays Presented to Sir Frederick Gowland Hopkins by Past and Present Members of His Laboratory. Edited by JOSEPH NEEDHAM and DAVID E. GREEN. Pp. 361; illustrated. Cambridge: At the University Press; New York: The Macmillan Company, 1939. Price, $4.75.

THIS is the third reprinting of these essays which were originally published in 1937 and presented to Sir Frederick Gowland Hopkins on the 75th anniversary of his birth. In the editors' introduction they state, "The aim of the writers of the following essays has been to indicate the most promising lines of advance in the various fields which they survey, and while maintaining a due standard of criticism, to speculate a little on the likely paths of future thought and discovery." The essays cover a very wide range of physiology taken in its broadest sense. They are very clearly written and in a sufficiently non-technical manner that anyone at all familiar with the physiologic sciences can profit by them. J. J.

INFECTIONS OF THE HAND. By LIONEL R. FIFIELD, F.R.C.S. ENG., Late Surgical Registrar and First Assistant and Demonstrator of Anatomy, London Hospital; Demonstrator of Minor Surgery, London Hospital. Second Edition by PATRICK CLARKSON, F.R.C.S. ENG., Surgical Tutor, Guy's Hospital; Demonstrator of Anatomy and of Operative Surgery, Guy's Hospital Medical School. Pp. 167; 57 illustrations, including 8 plates (2 colored). Second Edition. New York: Paul B. Hoeber, Inc., 1939. Price, $3.25.

IN the preface to the first edition of this book Mr. Fifield acknowledged his indebtedness to Kanavel and justified the publication of this work on the ground of the need for a "much smaller and simpler book for students, house-surgeons and practitioners." The second edition, which was completely rewritten and enlarged by Mr. Clarkson after the author's untimely death, can perhaps be similarly justified, though the Reviewer would hesitate to recommend the use of this book, rather than that of Kanavel, to any one interested in infections of the hand. It would seem that it would be possible for any one, student or practitioner, to find easily any information he desired in the larger monograph.

This is undoubtedly an excellent little volume, however, well illustrated and written, and for those who desire a small handbook this one can be recommended. I. R.

STERILITY AND IMPAIRED FERTILITY. Pathogenesis, Diagnosis, and Treatment. By CEDRIC LANE-ROBERTS, M.S., F.R.C.S., F.R.C.O.G., Gynecological Surgeon, Royal Northern Hospital; Consulting Obstetric Surgeon, Queen Charlotte's Hospital; ALBERT SHARMAN, M.D., M.R.C.O.G., Assistant Surgeon, Royal Samaritan Hospital for Women, Glasgow, KENNETH WALKER, F.R.C.S., Surgeon to the Genito-Urinary Department, Royal Northern Hospital, and to St. Paul's Hospital; and B. P. WIESNER, D.Sc., PH.D., F.R.S.E., Consulting Biologist, Royal Northern Hospital. With a Foreword by THE RT. HON. LORD HORDER, G.C.V.O., M.D., F.R.C.P. Pp. 419; 87 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, $5.50.

IN contradistinction to the usual book on sterility by a single author, the volume in review has been written by a group of two gynecologists, a urologist, and a biologist. The latter is particularly noted for his work on endocrinology. This group presentation of the subject makes for a well rounded out consideration of all aspects of sterility and impaired fertility. In a foreword, Lord Horder states that the three great advances in the subject of childless marriages in recent years, are researches into spermatogenesis and the morphology of spermatozoa, a great increase in our knowledge of the sex hormones and the introduction of new techniques in the investigation of tubal patency.

The book opens with a general survey of the problem, its terminology, incidence and general biologic factors concerned and the task of the physician who handles such cases. The authors introduce a new classification, dyskyesis, with a discussion of its significance. The influence of contraception on childless marriages is discussed and the eugenic factor is well handled.

The first five chapters of the book take up a discussion of the male factor in the childless marriage, with particular reference to the examination of the husband and his sexual history. A chapter on the constitution of the semen, one of the longest chapters in the book, brings out the biologic consideration of the spermatozoa, a discussion of the normal and abnormal types and the various factors influencing spermatogenesis. The great variability of head length, in their opinion, signifies abnormal spermatozoa.

They state that even grossly abnormal spermatozoa may exhibit normal motility and the capacity for propulsion is therefore, not a reliable index for normality.

The chapter on the Assay of Male Fertility makes practical use of the analysis and examination of the semen. The authors do not share the view of Randall and Wilson that inflammation of the prostate and seminal vesicles constitutes a very common cause of sterility.

The text proceeds further into a description of the male reproductive mechanism and its disturbances and the investigation of such disturbances. The authors state a preference for the technique of testicular biopsy used in the Squier Clinic. They regard acute orchitis of mumps and chronic orchitis of syphilis, as the two most important diseases of the testis with reference to sterility. In this section, as well as in a later chapter on the treatment of female sterility, there is a long discussion on the dietary disorders and dietary adjustments and a considerable discussion of vitamin E deficiency. They regard degeneration of the seminiferous epithelium caused by E-deficiency as irreversible. They regard vitamin E therapy as one of prevention rather than one of cure. Since no method of assessing vitamin E has been established they suggest the equivalent of 2½ to 5 gm. Wheat Germ Oil daily, or its concentrate equivalent. Various urologic operations are discussed in detail, as well as the use of hormones.

Whereas the male assay is positive in the inspection of the gametes, no similar procedure is possible in the female, and the authors discuss and describe the various measures to be used in the clinical and gynecologic examination of the infertile female partner. Modern physiology is detailed, recognition of the anovulatory cycle is discussed, and the diagnosis of physiologic, functional and pathologic causes are also thoroughly detailed.

There is an unusually elaborate discussion of the relationship of hormones to sterility and their use in infertile males and females. A series of appendices complete the book. These comprise case histories and technical details of practically all tests mentioned which are not otherwise discussed in the text. A well considered bibliography is appended.

This is one of the most thorough treatises on sterility and impaired fertility which has come to our notice. The group handling of the subject makes for completeness of discussion. The volume is highly recommended not only to the general practitioner or obstetrician, to whom childless women first come, but as well to the urologist who more and more frequently is being consulted, and to the biologist whose assistance is necessary in solving the finer points of the endocrine aspects of the problem.

P. W.

AN INTRODUCTION TO MEDICAL MYCOLOGY. By GEORGE M. LEWIS, M.D., Attending Dermatologist, New York Post-Graduate Medical School and Hospital, Columbia University; Instructor in Medicine (Dermatology), Cornell University, etc., and MARY E. HOPPER, M.S., Assistant in Mycology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. Pp. 315; 71 full-page plates. Chicago: The Year Book Publishers, Inc., 1939. Price, $5.50.

THIS is a volume which has been long and eagerly awaited by dermatologists. The subject matter is arranged primarily from the clinical angle, but there are shorter chapters on such phases as history, classification, structure and physiology, which give at least a smattering of the biology of fungi. A more lengthy chapter deals with the characteristics of pathogenic fungi which is entirely adequate to give the clinician an insight into the etiology of the mycoses that he handles. In line with the general policy to make the book useful in practice, particular emphasis has been placed on immunity and cutaneous sensitization. The body of the book is taken

up with the systematic discussion of first the superficial and then the deep mycoses. The bibliography is rich and up to date.

Laboratory methods are covered in a way that has not been accomplished in any book to date. Such phrases as the collection of materials, selection of instruments and glassware, the direct microscopic examination, the appearance of fungus in diseased material and even saprophytes and artefacts are discussed. Cultural methods and features, both gross and microscopic, occupy several short chapters. The use of Wood's light and the performance of the trichophytin test have not been neglected. In short, the subject of cutaneous mycoses has been completely covered, with special emphasis on the clinical aspects but without neglecting the laboratory ones.

The book is beautifully printed in large type and on enamel stock throughout. The illustrations are superlative. Although there are only 71 figures, many of them are broken up into perhaps a dozen smaller ones which are nevertheless so compactly arranged that the essential message is adequately conveyed. The authors have been remarkably successful in thus condensing a rich message in a remarkably small number of square inches of halftones. This applies to the illustrations both of clinical conditions and laboratory subjects. In short, the book is a model of completeness, accuracy, efficiency and artistry which no dermatologist can afford to do without. F. W.

PRIMER OF ALLERGY. A Guidebook for Those Who Must Find Their Way Through the Mazes of This Strange and Tantalizing State. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 140; illustrated (by John P. Tillery). St. Louis: The C. V. Mosby Company, 1939. Price, $1.50.

AFTER writing two editions of a book on allergy intended both for physicians and patients, the author has now written separate volumes for each, to the immeasurable advantage of both. This handy little volume, in addition to an adequate and lucid presentation of theoretical matters, contains a wealth of practical advice for allergics, amusingly written and illustrated. Physicians should recommend it to their allergic patients as an invaluable *vademecum*. R. K.

PROCTOLOGY FOR THE GENERAL PRACTITIONER. By FREDERICK C. SMITH, M.D., M.Sc. (Med.), F.A.P.S., Proctologist to St. Luke's and Children's Hospital, Philadelphia; formerly Associate in Proctology, Graduate School of Medicine, University of Pennsylvania. Pp. 386, 141 illustrations and 3 color plates. Philadelphia: F. A. Davis Company, 1939. Price, $4.50.

THIS book, planned to give the general practitioner the essentials of proctology, was written by a man who has had considerable experience in the proctologic surgery. It is essentially a compilation of facts from various works on the same subject, to which the author has added notes from his own experience. The illustrations are only fairly good and approximately two-thirds of them are reprints from other works on proctology. The first few chapters are given to anatomy and malformations of the rectum and anus, followed by chapters on diagnosis, treatment and anesthesia. The sections on the usual diseases of the perianal region and anal canal contain little that is new. The author still subscribes to the old idea that strangulated internal hemorrhoids should be treated conservatively. He includes a chapter on parasites of the lower bowel and one on diets. Throughout the book are numerous prescriptions, some of which are used by the author and others which have been culled from the literature. This book may serve its intended purpose of giving the general practitioner the essential facts of proctology. It does not, however, compare favorably with numerous recent texts on the same subject. L. F.

DISEASES OF THE MOUTH AND THEIR TREATMENT. A Text-book for Practitioners and Students of Medicine and Dentistry. By HERMANN PRINZ, A.M., D.D.S., M.D., D.Sc., DR. MED. DENT., Professor Emeritus of Materia Medica and Therapeutics, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania, Philadelphia, and SIGMUND S. GREENBAUM, B.S., M.D., F.A.C.P., Professor of Clinical Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania; Visiting Dermatologist, Mt. Sinai Hospital, Philadelphia General Hospital, Home of St. Michael's, and Eaglesville Sanatorium, etc. Pp. 670; 324 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, $9.00.

IT is commendable that a second edition should become necessary in a comparatively short time. New subjects have been added, namely lymphadenitis, Paget's disease, Schüller-Christian's disease, hereditary pseudohemophilia, sarcoidosis and others. The text continues to be uniformly good and the format and printing excellent. Most of the illustrations in color are poor (Plate 3, facing p. 210, is indeed grotesque) and mar an otherwise highly presentable volume. F. W.

OBSTETRICAL PRACTICE. By ALFRED C. BECK, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Pp. 858; 1043 illustrations. Second edition. Baltimore: The Williams & Wilkins Company, 1939. Price, $7.00.

THIS excellent textbook on the practice of obstetrics has been expanded by 155 pages of text in its second edition. Evidence of a comprehensive review of the literature appears particularly in the "Chapter on the Toxemias of Pregnancy" and in the three-fold increase in references included in the bibliography. A noteworthy and very timely expansion of the text regarding nutrition occurs in the subject matter of the "Management of Pregnancy." In spite of the addition of so much new material, the author has succeeded in retaining a personal note throughout. While the chapter on "Resuscitation of the Newborn Child" has been brought up to date, there is still lacking from the book a chapter on "Obstetric Injuries of the Newborn" and "The Diseases of Early Life," which might well be in place in a book of this character. Again the book is most warmly recommended as an outstanding text. P. W.

A SYNOPSIS OF REGIONAL ANATOMY. By T. B. JOHNSTON, M.D., Professor of Anatomy, University of London, Guy's Hospital Medical School. Pp. 462, 17 illustrations. Fourth edition. Philadelphia: Lea & Febiger, 1939. Price, $4.50.

THIS book was prepared by the author as an aid to his students in dissection. A very concise text, it is almost without illustrations because the author believes the student should refer to dissected parts rather than to illustrations in a dissecting manual for his information. He emphasizes that the book should not be consulted at all until the actual work of dissection has been completed. The only illustrations are diagrams of the nerve tracts of the spinal cord, brain stem and brain. The text follows in anatomical order as the dissection is carried out by the student. Each anatomical part is described, the important sections being emphasized with italics. There is little or no effort to make any practical application of the anatomy described. In the new edition a considerable revision of the material on the central nervous system has been added. The book is well printed. It should prove a considerable help as a handbook for students in dissections of anatomy. L. F.

PSYCHOBIOLOGY AND PSYCHIATRY. A Textbook of Normal and Abnormal Behavior. By WENDELL MUNCIE, M.D., Associate Professor of Psychiatry, Johns Hopkins University; Associate Psychiatrist, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital. With a Foreword by ADOLPH MEYER, M.D., LL.D., Sc.D., Henry Phipps Professor of Psychiatry and Director of the Department of Psychiatry, Johns Hopkins University. Pp. 739; 69 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, $8.00.

IT is said, "Psychobiology then is the study of those functions distinctively human, the things that man is best known for, the mentally integrated performances." In this psychiatric presentation of Adolph Meyer's psychobiologic concepts, frequent use is made of his novel, cartridge-shaped designs for life charts, where in the longitudinal dimension is shown the development and course of a disorder, while in cross section, such manifestations as may appear more suddenly, are depicted. With full clinical data plotted in this way, one unfamiliar with the system would need an interpreter.

The text is divided into four parts: Part I. Psychobiology—The Study of Normal Behavior. Historical and philosophical bases of psychobiology; student's personality study. Part II. Abnormal Behavior—Pathology and Psychiatry. Historical account; examination methods and immediate findings; detailed study of main reaction types (pathergasias); major reactions (holergasias); thymergasic reactions: elations; topical delusional states and para-reactions: parergasia; the support disorders (dysergasia); the acquired organic deficit reactions (anergasia). Part III. Treatment. General bases of treatment and procedure; important therapeutic aids; treatment of the major reactions (holergasias); para-reactions; dysergasic reactions; organic deficit states. Part IV. Historical Survey in Bibliography of the Development of the Concepts Underlying the Principal Reaction Sets (except the organic deficit states). Neurasthenia; hypochondriasis; anxiety states; obsessive-compulsive-ruminative-tension states; hysteria; manic-depressive psychoses; paranoia and paranoid conditions; parergasia; dysergasia. Part III, treatment, is mostly generalities; and in Part IV, two-thirds of the space is lost through blank, parallel columns. The term, dementia praecox, has most yielded to schizophrenia, and psychobiologists now wish it called, parergasia. One doubts if these new names for old diseases shall find general acceptance. The work is primarily for students but the more formal psychiatric books seem better adapted to their needs, perhaps with collateral excursions into psychobiologic psychiatry. Adolph Meyer is tireless, and the most original worker in the American school of psychiatry; but his somewhat nubulous presentations have not found great support beyond his devoted assistants. He does not appear to complete his works—perhaps the trait of a genius, as with Leonardo da Vinci. N. Y.

OFFICE GYNECOLOGY. By J. P. GREENHILL, B.S., M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Loyola University Medical School, Chicago; Professor of Gynecology, Cook County Graduate School of Medicine, etc. Pp. 406; 104 illustrations. Chicago: The Year Book Publishers, Inc., 1939. Price, $3.00.

IN this volume, "Office Gynecology," the author takes up many diagnostic or therapeutic procedures in gynecology which could be carried out in a medical office or clinic. Instructions are so definite and concise, the technique is so clearly described, illustrations so well correlated with the text, that the book should be of extreme value to the general practitioner. There are some procedures such as pneumoperitoneum and roentgenography, and colposcopic diagnosis of carcinoma of the cervix, which are beyond the scope of practice of the average practitioner, but are well

included in this book for the benefit of those whose ambulatory patients may be briefly hospitalized. One feels that the presentation of endocrinology in relation to gynecology is well given. It simplifies and will make clearly understandable to many men the confusion of terminology and treatment with which we have been flooded in the last few years. The book gives an excellent résumé of menstrual physiology and irregularities. A most timely chapter on "Premarital Advice" concludes the book. The suggestions contained in this chapter should do much to help the physician in his discussion with the 'about to be married' couple, who seeks his advice. A splendid presentation of the subject. P. W.

SLEEP AND WAKEFULNESS. As Alternating Phases in the Cycle of Existence. By NATHANIEL KLEITMAN, Department of Physiology, the University of Chicago. Pp. 638; 33 illustrations. Chicago: The University of Chicago Press, 1939. Price, $5.00.

THIS volume presents an exhaustive and competent treatment of the subject. The bibliography contains 1434 references. The discussion is eminently fair, moderately critical, and logically organized. For the researcher in the field the book is indispensable and for his sake we would not delete a line. Yet the final impression is disheartening; few problems have attracted so large a volume of research with so slight an advance toward their solution. G. McC.

PRACTICAL OBSTETRICS. By P. BROOKE BLAND, M.D., Emeritus Professor of Obstetrics, Jefferson Medical College; Consulting Obstetrician, Jefferson Medical College Hospital, Philadelphia, and THADDEUS L. MONTGOMERY, M.D., Clinical Professor of Obstetrics, Jefferson Medical College, Philadelphia. Pp. 877; 502 illustrations, including 27 colored plates. Third edition. Philadelphia: F. A. Davis Company, 1939. Price, $8.00.

THIS comprehensive volume in practical obstetrics which presents not only the ideas of the authors but many other well tested techniques in the practice of obstetrics, bears evidence of a thorough revision. Again, as in reviews of previous editions, it is warmly commended to the practitioner. P. W.

NEW BOOKS.

Viruses and Virus Diseases. By THOMAS M. RIVERS, M.D., Sc.D., Director, Hospital of The Rockefeller Institute for Medical Research, New York City. Lane Medical Lecture. (Stanford University Publications, University Series, Medical Sciences, Vol. IV, No. 1.) Pp. 133; 34 illustrations. Stanford University: Stanford University Press, 1939. Price, Paper, $1.75; Cloth, $2.50.

The New International Clinics, Vol. IV, N.S., No. 2, 1939. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 17 Collaborators. Pp. 339; illustrated. Philadelphia: J. B. Lippincott Company, 1939.

Fifteen "original contributions," with only two on sulfapyridine, the "clinics" and reviews of urinary lithiasis and ulcerative colitis make up this volume.

The Medical Clinics of North America, Vol. 23, No. 6 (Philadelphia Number —November, 1939) (Index Number). Pp. 329; 31 illustrations. Philadelphia: W. B. Saunders Company, 1939.

The symposium in this Philadelphia number includes 8 articles on metabolic diseases—mostly on diabetes. The other 10 articles cover the usually wide range of subjects—congenital syphilis, asthma, renal disease, drug addiction and so on.

Diagnostic Signs, Reflexes and Syndromes (Standardized). By Wm. Egbert Robertson, M.D., F.A.C.P., Visiting Physician, Medical Division, Philadelphia General, St. Luke's and Children's, and Northeastern Hospitals, and Harold F. Robertson, B.S., M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania; Assistant Visiting Physician, Medical Division Philadelphia General and Methodist Hospitals. Pp. 309. Philadelphia: F. A. Davis Company, 1939. Price, $3.50.

The Surgery of Injury and Plastic Repair. By Samuel Fomon, Ph.D., M.D., Formerly Major Medical Corps, U. S. Army. Pp. 1409; 925 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, $15.00.

Pathology. An Introduction to Medicine and Surgery. By J. Henry Dible, M.B. (Glas.), F.R.C.P. (Lond.), Professor of Pathology in the University of London (The British Post-Graduate Medical School); Late Professor of Pathology at the London School of Medicine for Women, etc., and Thomas B. Davie, B.A. (Cape), M.D. (L'pool), M.R.C.P. (Lond.), Professor of Pathology in the University of Liverpool; Late Professor of Pathology in the University of Bristol. Pp. 931; 374 illustrations including 8 plates in color. Philadelphia: The Blakiston Company, 1939. Price, $10.00.

The Fight on Cancer (Public Affairs Pamphlet, No. 38, 1939). By Clarence C. Little, Sc.D., Managing Director of the American Society for the Control of Cancer, Inc., and Director of the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me. Pp. 31; illustrated. New York: The American Society for the Control of Cancer, Inc., 1939. Price, 10c.

Harvey Cushing's Seventieth Birthday Party, April 8, 1939. Speeches, Letters, and Tributes. Pp. 146; 9 illustrations. Springfield, Ill.: Charles C Thomas, 1939, for The Harvey Cushing Society. Price, $3.00.

Vitamin D. Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations. By C. I. Reed, A.M., Ph.D., Associate Professor in Physiology, H. C. Struck, M.S., Ph.D., Associate in Physiology, and I. E. Steck, M.S., M.D., Instructor in Physiology and in Medicine, Department of Physiology and Department of Medicine, College of Medicine, University of Illinois, Arthritis Clinic, Illinois Research and Educational Hospitals. Pp. 389; 13 illustrations and 36 tables. Chicago: The University of Chicago Press, 1939. Price, $4.50.

Handbook of Skin Diseases. By Leon Hugh Warren, B.A., M.D., M.Sc. (Med.), Formerly Instructor in Dermatology and Syphilology at the School of Medicine, Temple University; Acting Assistant Surgeon (Dermatology) in the Office of Dermatoses Investigations of the United States Public Health Service, etc. With a Foreword by Frederick K. Weidman, M.D. Pp. 321. New York: Paul B. Hoeber, Inc., 1940. Price, $3.50.

NEW EDITIONS.

The Physiological Basis of Medical Practice. A University of Toronto Text in Applied Physiology. By Charles Herbert Best, M.A., M.D., D.Sc. (Lond.), F.R.S., F.R.C.P. (Canada), Professor and Head of Department of Physiology; Associate Director of the Connaught Laboratories; Research Associate in the Banting-Best Department of Medical Research, University of Toronto, and Norman Burke Taylor, M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lond.), Professor of Physiology, University of Toronto. Pp. 1872; 497 illustrations and 2 colored plates. Second Edition. Baltimore: The Williams & Wilkins Company, 1939. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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SOME PROBLEMS OF ACUTE INTESTINAL OBSTRUCTION.

ACUTE intestinal obstruction is a serious disease which is usually accompanied by a high mortality. The sequence of events leading to a fatal outcome has not been clearly understood, nor has any method of treatment been uniformly satisfactory.

A better understanding of various diseases has usually been accompanied by a decrease in the morbidity and mortality associated with these diseases. With a single exception within the last decade this has not been true in acute intestinal obstruction (Table 1). Schramm[41] reported a mortality in acute intestinal obstruction of 73% before 1873. In a series of cases during the following 10 years the mortality was 58%. That recent surveys of the subject have not afforded a more optimistic viewpoint is attested by the statement of Miller[32] who estimated in 1929 that the mortality from acute intestinal obstruction was approximately 61%. The data given in Table 1 indicate the great variation

TABLE 1.—MORTALITY IN ACUTE INTESTINAL OBSTRUCTION.

Author.	Date.	Cases.*	Mortality, %.	External hernia.	Mortality, %.
Gibson[22]	1900	646	47.0	354	34
Scudder[36b]	1908	121	60.0		
Richardson[36b]	1920	118	41.0		
Finney[18]	1921	245	36.0†		
Page[38]	1925	..	.....	539	12.2
Soutar[44]	1925	1655	38.2	1409	19.3
Van Buren and Smith[48]	1925	1089	41.0†?		
Miller[32]	1929	343	60.9†		
Vick[49]	1932	3625	38.8	3267	17.8
McIver[36b,c]	1932	156	44.0	147	18.0
Ssuscewski[45]	1933	121	38.8		
Achmatowicz[3]	1936	138	45.5		
Wangensteen[51]	1939	111	17.1	45	20.0

* Exclusive of external herniæ.
† Includes external herniæ.

in mortality rates reported by various authors. The data as a whole show little improvement in mortality although our knowledge of the pathologic physiology of gut obstruction has been greatly extended.

McIver[30b] reviewed 3 series of cases over different 10-year periods in the Massachusetts General Hospital; the mortality from 1898–1907 was 60%; from 1908–1917, 41%; and from 1918–1927, 44%.

Several difficulties arise in the analysis of large numbers of cases from the literature. The most obvious of these is that the various series are not always comparable. Acute intestinal obstruction is not a single clinical entity but is actually a collection of conditions with certain common factors. The most obvious are the inability of the gut to propel its content untrammeled throughout its entire length, and the development of distention of the intestine. Variations in etiologic factors, such as the site of obstruction, integrity of blood supply, general condition of the patient before onset, and the length of time elapsed between onset and beginning of treatment, influence the mortality rate regardless of the effects of operative treatment.

Etiologic factors in the initiation of mechanical obstruction of the bowel have long been well understood. Clear descriptions of causation are to be found in the works of Brinton[11] in 1867 and Treves[47] in 1884. Approximately half of all the cases of intestinal obstruction are caused by protrusion of the intestine through external hernial orifices. This has been well borne out by many published statistics. Inguinal and femoral herniæ are the most common offenders in this regard;[30a] according to Vick[49] who studied a large series (6892 cases) approximately 88% of all obstructions from herniæ were due to incarcerations of gut in these regions. The mortality associated with obstruction due to hernia is low as compared to that due to most other causes, even though the incidence of strangulation is likely to be high. The obvious reason for this lower mortality is that the diagnosis is made early and a standard procedure, early operation, is not usually unduly delayed. In addition, the operation is likely to be simpler since the lesion is not difficult to find. Therefore in reported series which exclude cases caused by external hernia, the total mortality from intestinal obstruction is expected to be higher than in those in which these are included.

Next to external hernia, the most common etiologic factor is adhesions and of these, adhesions resulting from previous surgical procedures form the largest group in this category. McIver[30b] has indicated that in the affected group found early in the postoperative period the mortality is higher than in those cases occurring sometime after operation. This is despite the fact that these cases usually have not left the hospital when they become obstructed and are therefore not to be classed as seeking aid late in the disease. These two conditions, external hernia and adhesions, account for approximately three-fourths of all cases of acute intestinal obstruction.

Obstructions which are likely to be associated with interference with the mesenteric blood supply are as a rule more serious in nature since, in addition to the possibility of necrosis and perforation of the intestine, there is a greater tendency to early toxemia and shock.

The high mortality in most published series is no intimation that decided effort has not been made to understand the cause of death in acute intestinal obstruction. A considerable amount of clinical and laboratory investigation has been expended upon this problem. Three main theses have been advanced to explain the cause of death in this condition.

The oldest theory concerning the cause of death in intestinal obstruction is that a potent toxin is formed. The possibilities for the production of this toxic material are: 1, that the bacteria, particularly *Welch bacilli*, elaborate a specific toxin[34,58] and that specific antitoxins are effective in protecting against this toxin[7] (this viewpoint is contested by Owings and McIntosh[37] and Oughterson and Powers[36] who could find no protective action of *B. Welchii* antitoxin in experimental animals); 2, that the toxin results from an abnormal mucosa or secretions into the gut;[16,55a,b,c] 3, that the toxin arises as the result of bacterial growth in the obstructed gut and is not specific;[13,15,35] 4, that the toxin is formed from putrefaction of intestinal content;[4] and that 5, the symptoms of toxemia actually are the results of bacteria migrating from the obstructed loop causing a bacteremia, as suggested by Borszeky and Genersich in 1902.[6] This latter view was promptly and effectively refuted by Clairmont and Ranzi.[13] The nature of the toxic substance is likewise a much debated subject as is also the mode of its transmission from the intestine.

The concept that in simple obstruction death results from loss of fluids and salt has received considerable consideration since it was shown by Hartwell and Hoguet[24] and McLean and Andries[31] that animals with obstructed loops of bowel survived longer if a saline solution was administered. That the problem of fluid and salt loss is an important one in these cases has been referred to by Hayden and Orr,[25] Gamble and McIver,[20] White and Fender[56] and many others. That it is the sole cause of death is doubtful since, while survival time is increased by the administration of salt solution, death nevertheless occurs. In those cases in which strangulation is a factor, death occurs early even in animals well hydrated.

The fact that late in the disease patients with acute intestinal obstruction appear similar to patients in shock, has suggested that there is some relationship between the two conditions. The concept suggested by Braun and Boruttau in 1908[9] and occasionally referred to by others[19,57] that the element of shock was quite important in explaining the cause of death in intestinal obstruction, has recently received some attention in German literature. An additional article by Braun in 1925[8] reiterated the concept that associated with occlusion there is strong nervous stimulation which is increased by the addition of physical and chemical stimulation from the altered intestinal content. These stimuli are supposedly mediated not only through reflexes of nerves in the intestine and associated autonomic ganglia, but also act centrally. There results a true picture of shock with associated fluid loss, blood concentration, and capillary stasis.

Gudladt[23] who accepts this concept, has, as recently as 1939, reported on pathologic findings in 190 cases of intestinal obstruction. He feels that his findings support the view that the cause of death is associated with damage to the circulation. However, he also reports changes in the lungs which appear to support the concept of Becher[5] that the lung plays an important rôle in detoxifying substances absorbed from the intestine. Scudder, Zwemer, and Whipple[43] reported results on studies of the potassium content of blood in intestinal obstruction, and point out that acute intestinal obstruction and adrenal insufficiency have many features in common. Scudder, Zwemer, and Truszkowski[42]

reported an elevation in the level of potassium in the blood of cats following obstruction, and suggest that a high potassium level might be the cause of death. This has likewise been reported by Cutler and Pijoan[14] in the dog. However, in the study of human cases Falconer, Osterberg, and Bargen[17] did not substantiate these findings. In fact, they noted a fall in the potassium content in the serum and suggest, as did also Scudder, Zwemer, and Whipple,[43] that potassium is actually lost through secretions from the upper intestinal tract.

Within recent years there has been a renewal of interest in the part that distention plays in the cause of death from intestinal obstruction. As an important finding in late cases of intestinal obstruction, distention is stressed as a predominating feature in diagnosis. The rôle that distention plays in the train of events which leads to a fatal outcome in these cases, while referred to by most authors, has not received attention commensurate with its importance until the last decade. Burget, Martzloff, Thornton, and Suckow,[12] Herrin and Meek,[26] and Taylor, Weld, and Harrison[46] stressed the importance of distention *per se*, with regard to the initiation of symptoms and to recovery of animals with experimentally produced obstruction. Burget and coworkers[12] showed that if a closed loop obstruction was kept decompressed no symptoms of obstruction resulted. Herrin and Meek[26] and Taylor, Weld, and Harrison[46] presented experimental data to support the close relationship between the course of events in obstruction and the distention, and indicated that it was possible to cause the entire picture shown by animals with obstructed loops, when no obstruction was present, provided distention of the gut was produced.

Wangensteen and his associates have done much to focus attention upon the rôle of distention as a factor of great importance in acute intestinal obstruction. The initiation of the use of suction drainage in the treatment of acute intestinal obstruction while popularized by these workers, has been sporadically suggested for many years.[52,53] Suction drainage by use of gastric or duodenal tubes is but one method for accomplishing relief of distention of the small bowel. Unfortunately, the method rather than the principle has been regarded as fundamentally important, and we find many who condemn or praise the method without consideration of the basic principles involved. Reiterating these principles, Wangensteen[51] has reported mortality statistics of cases treated by suction drainage which attest to the efficacy of the method but it is to be noted that the cases so treated were a group, most of whom were suitable for this type of treatment, and other cases were submitted to various operative procedures.

In 1938 Abbott and Johnston[2] reported the use of intestinal intubation in the treatment of simple intestinal obstruction by the use of a tube developed by Miller and Abbott.[33] The rationale of its use was based on the proposition that the distended intestine could be decompressed better with suction applied directly above the point of obstruction than at higher levels. This, in effect, is tantamount to an enterostomy without the necessity of an operative procedure. In addition to drainage from a vantage point it permits the feeding of the patient. Further studies with this method have indicated its usefulness, not only with regard to the treatment of intestinal obstruction,

but also for localization of the obstructing lesion[1a,b,27,28a,b,29] and for the preparation of the patient for operation. Sufficient experience has been gained with the use of intestinal intubation in the treatment of simple intestinal obstruction and adynamic ileus to illustrate its efficacy. In several clinics where it has been used extensively, but judiciously (Hospital of the University of Pennsylvania, Detroit Receiving Hospital, and Presbyterian Hospital in New York), there has resulted a marked reduction of the mortality rate from acute intestinal obstruction. For the past 2½ years the mortality from small intestinal obstruction at the Detroit Receiving Hospital, including all cases of intestinal obstruction whether the obstruction contributed to the death or not (except those due to strangulated external hernia) has been approximately 23.9%. The mortality from simple acute obstruction treated by intubation was 9%. Similar good results have been attained at the Presbyterian Hospital.[54] The limitations of the method and difficulties of its use as well as its advantages are set forth in publications of Abbott and his associates[1a,2] and Johnston and his associates.[2,28a,b,29,39]

It is not possible at present to obtain an adequate appraisal of the effect which the judicious use of suction drainage has had on the mortality from small bowel obstruction. It is much too early, since its place in therapy was enunciated by Wangensteen and since the introduction of drainage from the lower reaches of the bowel, to allow for large series to have been reported. It is to be recognized as significant that in comparison to older statistics, those presented by Wangensteen and associates[51] have a decidedly lower mortality, and we have been able to bring about a further decrease in the mortality of our own cases. It is worthy of note that Wangensteen[51] has surveyed all types of cases of small bowel obstruction and reports a mortality of 17.9%, reducing the mortality from obstructions within the abdomen to below that commonly attained in those cases associated with external hernia. The cases reported by Wangensteen were not a personal series but were cared for by several individuals. However, this group of surgeons must recognize the place of suction drainage in the broad problem of the therapy of intestinal obstruction, based on an understanding of the pathology and physiology involved. The problem of treatment of this condition must be based on principles involved without regard to strict adherence to any method. The well-known saying that "the sun should never set on an unoperated case of intestinal obstruction" is as erroneous and as productive of poor results as such general dicta are likely to be, if followed strictly. Wangensteen[51] has pointed out that there is a mortality of treatment as well as of disease, a fact which is too often ignored. Treatment carried out on the basis of dicta, or fixed routine, without regard to the pathologic lesion and physiologic principles involved, and without the consideration of obstruction of the bowel as a diversified problem, must lead to many unnecessary fatalities.

An additional method of decompressing the distended intestine has been suggested by Rosenfeld and Fine[40] who found that in cats it was possible to cause a marked decrease in intraluminal pressure produced by distention of air or nitrogen if the animals were made to breathe pure oxygen. This procedure offers promise for use in intestinal ob-

struction, even though it is likely to be slow in its action in decreasing the amount of gas present, because of the salutory effects offered in more effective oxygenation in a patient whose respiratory activity is hampered by distention.

Regardless of the possibilities for the reduction in mortality from intestinal obstruction by careful consideration and use of suitable methods of treatment, it is not likely that the mortality from this condition will be lowered materially until the importance of early diagnosis is universally recognized.[50] Within a few hours after the onset of obstruction, when distention is likely to be slight, operation is attended by low mortality.[10,32] When distention is marked, dehydration present, and changes in blood chlorides and urea are marked, the difficulties of treatment are greatly increased. It is well to point out that in addition to the recognition of the early symptoms of intestinal obstruction the Roentgen ray offers early diagnostic aid. The use of contrast media is not necessary, but actually contraindicated early in the disease. In fact, Roentgen ray without contrast media offers the only early laboratory finding of any advantage, and should be utilized in all suspected cases. While the upright film may reveal fluid levels and indicate the presence of obstruction, the supine film will in many instances indicate the level of the obstruction. When the diagnosis of obstruction is established early, before marked distention and dehydration are present, operation ought not to be delayed.

Early diagnosis and treatment, so important in simple acute obstruction, becomes imperative in those cases where there is interference with the mesenteric blood supply, not only because of the possibility of releasing the occlusion to the vessel early, thereby preventing necrosis of the bowel, but for the prevention of the development of the severe toxemia which is so rapidly fatal, The early differentiation between simple and strangulated obstruction is not easy. The diagnosis of strangulation is based on the severity of the onset, the rapidity of progression of symptoms, evidence of a localized gas-filled loop, and symptoms out of proportion to the amount of distention present. Increasing pulse rate, falling blood pressure, and presence of localized tenderness are likely to be found late and should always suggest strangulation. Gatch[21] has suggested that it is possible to treat such patients without operation until the strangulated loop becomes well walled off as is practiced in cases of appendiceal abscess, but we have not felt that it is wise to defer operation in cases of suspected strangulation. Preparation by blood transfusion, intravenous saline solutions, and the insertion of a tube at least into the stomach, need not delay operation long and are important aids.

Consideration of the importance of distention as the initiating factor in the sequence of events following simple acute obstruction of the bowel does not imply any particular form of therapy. Relief of distention can be brought about by operation or by removal of the distending content from within the bowel by means of intubation. Which of these methods is to be used depends upon the problems presented by the patient and not by custom. There have undoubtedly been instances where an attempt has been made to apply suction drainage for treatment of intestinal obstruction without regard to the problem presented by the patient and it is to be expected that such attempts

will be disheartening. The concept that suction drainage is a specific regimen for intestinal obstruction is but little less dangerous than the concept that early operation is indicated in all forms of intestinal obstruction. It is only by early diagnosis, a consideration of the underlying principles involved, the conscientious appraisal of the patient, and the utilization of the best available forms of treatment—that the unnecessarily high mortality from intestinal obstruction will be effectively lowered.

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OPHTHALMOLOGY

UNDER THE CHARGE OF
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THROMBO-ANGIITIS OBLITERANS OF THE RETINAL VESSELS.

In this section for August, 1935, the subject of recurrent hemorrhages into the retina and vitreous was reviewed. At that time it was stated that in most cases of this syndrome in the young adult the causative lesion was thought to be tuberculous periphlebitis of the retinal veins. Attention was called to the occurrence of an essentially identical lesion in patients with diabetes mellitus in whom no definite etiologic factor aside from the diabetes could be discovered. Recently Friedenwald has called attention to the possibility that the basic cause of the hemorrhages in this latter group of cases is an increase in capillary fragility dependent on an improper utilization of vitamin C, associated in some way with a deficiency in vitamin B complex. It was pointed out that in certain non-diabetic cases in which the diagnosis of tuberculosis of the retinal vessels seemed unlikely, the cause of the lesion had been assigned by various authors to focal infection and rather vague endocrine or circulatory disturbances. A few cases can be proved to be due to syphilis. In the majority of cases when the vitreous is sufficiently clear to allow careful study of the retina, local lesions in the retinal vessels, usually the veins, can be seen to be the source of the bleeding. In a fairly large number, however, the exact cause of the local vascular lesion remains in doubt. At the time of writing this review I was not acquainted with the studies of Marchesani[9a,b] which were published in the latter part of 1934 and in 1935.

It is of interest that in reporting on a case of hemorrhage into the vitreous before the Ophthalmological Society of the United Kingdom in 1881, Jonathan Hutchinson[3] stated that his patient, a young man of 24, had had frequent epistaxis, cold feet, vague pains simulating gout, pain in the heel which prevented him from walking at times, "rheumatic" pains in the fingers and toes, and a "numb tingling" in the thumbs. Marchesani was impressed by the difficulty of demonstrating the presence of tuberculosis in other parts of the body in the majority of his patients with recurrent hemorrhages into the vitreous. He noted that many of them complained of symptoms similar to those described by Hutchinson and, in addition, often of transitory severe cyanosis of the extremities and trophic disturbances in the nails and skin. Pulsations were absent in one or more of the arteries of the lower extremities of a number of the patients. All of them showed definite changes in the nail-fold capillaries, such as widening of the intercalary space, dilatation of the venous loops, and spontaneous capillary hemorrhages. In his opinion, a disease which affects only the vascular system, runs its course without marked evidences of inflammation, and does not lead to a destructive lesion of the tissues of the eye cannot be considered to be tuberculosis. Because of the evidences of a more or

less generalized disturbance of the vascular system in these individuals, Marchesani believes that the vascular lesions in the retina responsible for recurrent hemorrhages into the vitreous represent an ocular manifestation of thrombo-angiitis obliterans (Buerger's disease). He admits that the coincident occurrence of retinal periphlebitis with manifest gangrene of the extremities is rare. He based his conclusions on the study of a series of 22 patients, 2 of whom had gangrene of toes and 1 gangrene of fingers; 19 of the patients were thought to have evidences of latent Buerger's disease.

Marchesani further supported his views by his interpretation of the histologic findings in the eye of one of the patients with gangrene. He found that the lumens of the smallest retinal vessels were variably narrowed as a result of a homogeneous structureless swelling of the subendothelial tissues. In some of the larger vessels, both arteries and veins, the endothelial layer was destroyed and the lumen was filled with a cell-poor or cell-free fibrin-like mass of homogeneous or network structure. Around these vessels there had been some extravasation of red blood cells and some increase in the glial fibers with only a few cells of inflammatory type. In other vessels the lumen was filled with granulation tissue rich in cells of endothelial character with some evidences of recanalization. There was some splitting up of the lamina elastica but the rest of the wall was not abnormal. Vessels in the iris and ciliary body were involved as well as those in the retina. In some of the vessels at the limbus a non-specific perivascular infiltration with round cells was present. According to Marchesani, these vessel changes are similar to those described by other authors in the extremities, internal organs and brain in patients with Buerger's disease. Marchesani discussed also the histologic findings in a case reported by Fleischer as one of tuberculosis of the retina. Marchesani thought that the endothelial proliferation with scattered points of occlusion of the lumen and the cellular proliferation in the vessel sheaths described by Fleischer were evidence of thrombo-angiitis obliterans, and that the nodules considered by Fleischer to be tubercles were really occluded vessels.

In 1938 Marchesani[8c] reported the histologic findings in 2 other eyes, the lesions in which had been diagnosed by him as thrombo-angiitis obliterans of the retinal vessels. In one with recurrent hemorrhages into the vitreous the retinal vessels near the disk showed hyaline thickening of the walls. This hyaline thickening increased in degree in the distal parts of the vessels, especially the veins, so that in some spots the lumen was almost obliterated. In most of the peripheral vessels, however, the lumen was completely filled with a cell-poor fibrin-like tissue with occasional cellular proliferations suggesting recanalization of the lumen. In the other, apparently a postspastic occlusion of the central artery of the retina, the central artery of the retina and its branches showed severe wall changes with marked narrowing of the lumen but without complete closure at any point. These changes were in part in the nature of hyaline thickening with localized endothelial proliferation and in part apparently homogeneous thrombus formation in the lumen firmly attached to the wall. Similar changes were found in the cerebral vessels.

In 1934 Stauder[14] called attention to a group of cases simulating mul-

tiple sclerosis which he believed to be really thrombo-angiitis of the cerebral vessels. In a paper published in collaboration with Marchesani[9] in 1935, Stauder reported that 3 of Marchesani's 20 patients with primary symptoms of retinal periphlebitis showed this central nervous system syndrome of atypical multiple sclerosis. Also 5 cases which were seen primarily by the internist or neurologist showed lesions suggestive of thrombo-angiitis of the retinal vessels. In 3 of these the typical syndrome of retinal periphlebitis with recurrent hemorrhages into the vitreous and retinitis proliferans was present. In Stauder's opinion, the 2 cases reported by Löwenstein as tuberculosis of the cerebral vessels and of the eye and the 6 cases of ophthalmo-encephalomyelitis reported by ter Braak and van Herwaarden, 2 of which showed typical retinal periphlebitis, are further examples of cerebral and retinal thrombo-angiitis obliterans.

Marchesani's conception of the nature of this rather puzzling syndrome of recurrent hemorrhages into the vitreous is at least an interesting one even if it cannot be considered as definitely proved as yet. Personally, I have seen thrombosis of the retinal veins in a few of a rather large series of patients with typical Buerger's disease of the extremities. Also 1 patient, seen originally because of recurrent hemorrhages into the vitreous, returned several years later with the characteristic picture of thrombo-angiitis of the lower extremities. Although he had no subjective eye complaints at the second visit and no hemorrhagic extravasations were found in the vitreous, active periphlebitis with hemorrhage was still present in each retina.

Since Marchesani's original publication, several other authors have reported essential agreement with his conclusions. In 1935 Ludwig[7] reported a case of recurrent hemorrhage into the vitreous on the basis of disease of the smaller arterial and venous branches with aneurysmal dilatation and new vessel formation, but without perivascular lesions or focal lesions in the retina or choroid. This patient was believed to have Buerger's disease because of the additional presence of paresthesias of the hands and feet and changes in the capillaries of the nail-fold characteristic of a vasoneurosis. Also in 1935, Gilbert[1] reported 2 cases, 1 with a closure of the inferior temporal branch artery and 1 with perivasculitis of the inferior temporal branch artery and vein, both of whom developed later thromboses in the lower extremities. He stated that Buerger's disease must be thought of as the possible etiologic factor in otherwise unexplained instances of closure of the central or branch arteries of the retina. In 1936 Mikuni[11] stated that in his clinical observations retinal periphlebitis and thrombo-angiitis obliterans in other parts of the body were at times coincident. He was able to find evidences of Buerger's disease in 2 of 7 patients with retinitis proliferans. In his ophthalmoscopic studies of 5 patients with Buerger's disease, he found retinitis proliferans in 1. In 1937 Lisch[6a] reported a closure of the central artery of the retina in a man 33 years of age, which he believed to be due to thrombo-angiitis obliterans since the man had gangrene of the toes, barely palpable dorsalis pedis arteries, and changes in the nail-fold capillaries. In 1937 Schmelzer[13] reported that he had examined 6 cases of classical thrombo-angiitis obliterans with gangrene of the extremities, in none of whom was there evidence of recurrent hemorrhages into the vitreous. One of the patients, how-

ever, had had a closure of the central artery of the right eye 4 years before. Schmelzer thought, therefore, that closure of the central artery of the retina or one of its branches in a relatively young, otherwise healthy adult might be an early sign of a progressive thrombo-angiitis obliterans. In 1938 van Rijsewijk[17] suggested the possibility of Buerger's disease in a case with recurrent hemorrhages into the vitreous and Jacksonian epilepsy. Radnót stated that Lange and Birnbaum also confirmed Marchesani's findings.

Two histologic studies also have been published in which the authors agree with Marchesani's interpretation of the lesions in the retinal vessels. In 1937 Uyama[16] reported 2 cases which he diagnosed clinically as thrombo-angiitis obliterans of the retinal vessels. In one of these cases histologic examination showed that the walls of the smaller retinal arteries were thickened, the lamina elastica hyperplastic, and that there were increased collagenous and elastic fibers in the ground substance of the intima. The lumens were lined by normal or swollen endothelial cells but were markedly narrowed or closed by the thickening of the walls. The lumens of the larger arteries were filled with blood corpuscles and homogeneous fibrin-like masses containing some epithelioid cells suggestive of thrombosis. The walls of the veins were thickened but the lumens were not occluded and the capillary walls were thickened also. Uyama thought that this picture corresponded to the first form of intimal proliferation described by Jäger in endangiitis obliterans. In 1938 Maul[10] reported the case of a man, aged 56, who suffered from definite Buerger's disease of the extremities, and who had a unilateral optic atrophy secondary to closure of the central artery of the retina. Histologically, the central artery of the retina, and to a less extent the central vein, showed subendothelial proliferation and patchy endothelial proliferation. In the central artery there was a homogeneous firmly attached thrombus. Similar changes were present in the walls of the cerebral vessels.

There has been also considerable opposition to the acceptance of Marchesani's views on the basic nature of these perivascular and occlusive lesions of the retinal vessels, particularly by those authors who believe that recurrent hemorrhages into the vitreous in young adults are due always to tuberculosis of the retinal vessels. In 1935 Kokott[5] reported that among 5 clinical cases of retinal periphlebitis with recurrent hemorrhages into the vitreous 2 were definitely proven to be tuberculous and 1 was probably tuberculous. Two of the patients had no demonstrable systemic disease. In none were there any signs of Buerger's disease. Also in 1935 Knapp[4] reported no evidence of Buerger's disease in 1 case and von Hippel[2] stated that among 11 cases of Buerger's disease of the cerebral vessels reported by Jäger and confirmed at necropsy, there was no instance of retinal periphlebitis. In 1937 Radnót reported that among 6 cases of retinal periphlebitis none showed any clinical evidence of Buerger's disease while 3 showed healed pulmonary tuberculosis. In the discussion Radnót stated that Löwenstein, Petragnani, Schreck, Bonnet, Paufique and Vogt had not found any evidence of Buerger's disease in their patients with retinal periphlebitis. In 1939 Lisch[6b] studied ophthalmoscopically 35 cases of various forms of peripheral vascular disease, among which there were 5 cases of thrombo-angiitis obliterans. He found no evidence of retinal periphlebitis in

any of these cases, and consequently does not believe that vascular disease of the Buerger type plays an important rôle in the etiology of recurrent hemorrhages into the vitreous.

Considerable histologic evidence also has been adduced to controvert Marchesani's conception. It is well known that perivenous lesions can be produced in the retina of experimental animals by the injection of living tubercle bacilli into the carotid artery. Recent confirmation of these results was furnished by Uyama who first sensitized rabbits by the subcutaneous injection of tuberculous antigens and then injected living tubercle bacilli into the left heart. In his series of 26 animals so treated, 4 developed retinal periphlebitis. The lesions showed lymphocytes and endothelial cells but no giant cells or caseation. In 1935 von Hippel examined histologically an eye enucleated because of secondary glaucoma following recurrent hemorrhages into the vitreous. He found short stretches of two retinal arteries closed by intimal proliferation in which epithelioid and giant cells were present. The retinal veins showed perivascular infiltration, partly mononuclear round cells, partly nodular collections of epithelioid cells, round cells, and occasional giant cells. In some spots the lumen of a vessel was completely or almost completely closed by cellular proliferation of indeterminate type, possibly an organized but not a recanalized thrombus. In the choroid there was a characteristic tuberculous nodule with caseation necrosis of the overlying retina. A vessel in the iris was completely closed by lymphocytic infiltration. There was round cell infiltration of the wall of the central vein of the retina with narrowing but not obliteration of the lumen. No tubercle bacilli were demonstrated, but the case was considered to be definitely ocular tuberculosis. Von Hippel considers Buerger's disease to be a non-specific occlusive and inflammatory disease of the vessel walls. He does not deny that such non-specific vessel wall disease may occur in the retina. But, since he can find this type of vessel lesion in cases which show definite tuberculosis in other tissues of the eye, he is inclined to believe that tuberculosis is the etiologic factor in the majority of cases of this type.

In 1937 Suganuma[15] reported the case of a girl, aged 21 years, who had recurrent hemorrhages into the retina and vitreous of the right eye with retinitis proliferans. In the left eye there was a sclero-keratoiritis, clinically of tuberculous type. By roentgenogram there was infiltration of the apices of both lungs. Later iritis and secondary glaucoma developed in the right eye and the eye was enucleated. Histologically, there was a periphlebitic patch in the equatorial region of the retina. This was made up centrally of epithelioid cells and peripherally of round cells with giant cells in the intermediate zone. The vein was not thrombosed. There was an exudative mass of epithelioid cells which broke through into the vitreous. On the inner surface of the retina there was a proliferated band of connective tissue, glial fibers and blood-vessels. A small patch of epithelioid cells was found surrounding a choroidal artery. In the anterior segment of the eye nodules of epithelioid and giant cells were present in the iris, ciliary body and cornea. The case was considered to be one of ocular tuberculosis.

Also in 1937 Radnót reviewed the arguments for and against the occurrence of the Buerger type of thrombo-angiitis obliterans in the retinal vessels. Noting that Gilbert had demonstrated tubercle bacilli

in a case of retinal periphlebitis, she makes a distinction between lesions which are primarily perivascular in type and location and those which affect the vessel wall itself primarily. She reports on the histologic examination of 5 cases. Four of these cases showed definite periphlebitic lesions which were considered to be tuberculous. The inflammatory changes were located entirely outside the vessel wall, the wall itself being unaffected. The lumen of the vessel was compressed or even obliterated by the pressure of the granulation tissue around the periphery of the vessel. In the fifth case there was a primary lesion of the vessel walls, especially of the media. There was a hyaline degeneration of the middle layer leading in places to closure of the lumen. In other places the vessel seemed to be converted into a nodule of non-specific granulation tissue. There was no apparent lesion of the intima. In Radnót's opinion the lesions in this last case might be considered to simulate the picture of thrombo-angiitis obliterans of the peripheral vessels.

In summary, it might be said that in the vast majority of the cases, at least, the basic local lesion underlying recurrent hemorrhagic extravasations into the vitreous is a diseased condition in the walls of the retinal vessels, predominantly or primarily in most, if not all instances, in the veins. The distinction between a primarily perivenous and a primarily venous or arterial lesion may be an important one from the etiologic standpoint. An attempt should be made to differentiate these lesions ophthalmoscopically where the vitreous is sufficiently clear to allow careful study of the retinal vessels. A certain number of the cases, particularly of those of perivenous type, may be due to tuberculosis, either primary in the retina or secondary to a hidden or latent focus of tuberculosis in the choroid. In perhaps a larger number of cases in which tuberculosis cannot be demonstrated elsewhere in the body, there may be a primary non-specific inflammatory or degenerative lesion of the vessel walls. This lesion may be the retinal counterpart of Buerger's disease and may be confined to the retinal vessels or at times may be associated with similar lesions in other parts of the body. In certain cases of closure of the central artery of the retina, the basic lesion may be a primary disease of the vessel wall simulating or related to thrombo-angiitis obliterans.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF DECEMBER 19, 1939

Distribution of Water and Serum Electrolytes in Experimental Diabetes Mellitus. F. WILLIAM SUNDERMAN and F. C. DOHAN (Department of Research Medicine, Pepper Laboratory and Cox Institute, University Hospital). Measurements of serum volume, extracellular fluid and concentrations of serum components were made in depancreatized dogs that had been permitted to go into ketosis following the withdrawal of insulin. Since the depancreatized animals suffered marked reduction in body weight, for comparison similar measurements were made following ketosis from simple starvation.

In the depancreatized dogs the average serum volume calculated in relation to the body weight was approximately 29% greater during ketosis than during the control period, although the total serum volume was approximately 10% less during ketosis than during the control period. In ketosis from starvation the total serum volume was decreased in proportion to the reduction in weight and within the limits of error of the measurements the serum volume in relation to body weight was unchanged.

The actual quantities of total base, chloride, bicarbonate and protein in the circulating serum were decreased during ketosis in the depancreatized animals although the amounts of these components, with the exception of bicarbonate, when expressed in relation to body weight were all increased.

The studies suggest that the dehydration observed in experimental diabetes mellitus induced by pancreatectomy in dogs is not made at the expense of serum volume or of the extracellular fluids but rather at that of the intracellular fluids.

Mechanism of the Diuresis Produced by Acacia. ARNOLDUS GOUDSMIT, JR. (Laboratory of Physiology, School of Medicine, University of Pennsylvania). The present report incorporates the results of clinical and experimental observations gathered at the Mayo Clinic and Foundation, in collaboration with Drs. Binger, Power, Keith and Bollman. Injections of acacia may be followed by the mobilization of edema fluid and its elimination with the urine in patients suffering from the nephrotic syndrome. A good diuretic response was obtained in 36 out of 40 consecutive cases in which this form of treatment was used.

The colloid osmotic pressure of the serum examined after completion of a course of injections of acacia was increased as compared to its level before treatment in only 43% of 28 cases in which it was determined. It was essentially unchanged in 39% and actually decreased in 28%. As a consequence of the injection of acacia the volume of the plasma increases, its constituents are diluted and it depends on the relationship of the diminution of concentration of the serum proteins and the concentration of acacia in the plasma what net changes in

colloid osmotic pressure actually take place. There was no correlation between the direction of the change of colloid osmotic pressure and the clinical response (diuresis or absence of it).

Experiments on dogs were therefore performed, testing whether acacia might alter the permeability of the kidney. It was found that the rate of glomerular filtration (creatinine clearance) was essentially unchanged; but the rate of excretion of chloride was significantly increased, an average of 189%. Subsequently, a study of patients receiving acacia revealed similar increases in the absolute amount of chloride excreted per 24 hours, and sometimes also of its concentration in the urine.

It is well to remember that a very important disturbance of the function of the kidney in the nephrotic syndrome is its inability to excrete all sodium chloride and water ingested. The consequent accumulation of these substances leads to the appearance of edema. It is difficult to conceive how the diminished concentration of protein in the serum and the decreased colloid osmotic pressure could be held directly responsible for what appears to be an abnormally large tubular reabsorption of water and sodium chloride. Whatever its explanation, it would seem that acacia helps in the reduction of tubular reabsorption of chloride and water to a more normal level.

Studies on the Molecular Weight of Diphtheria Toxin, Antitoxin and Reaction Products. A. M. PAPPENHEIMER, JR. (Antitoxin and Vaccine Laboratory, Jamaica Plain, Mass., and Department of Bacteriology, University of Pennsylvania). Preparations of diphtheria antitoxic horse pseudoglobulin have been made of which 43.5% of the nitrogen is specifically precipitable by toxin. These preparations behave in every way, except immunologically, as a single molecular species; they are extremely homogeneous by sedimentation, electrophoresis and diffusion. Although the molecular weight of antitoxin as calculated from the sedimentation-diffusion data does not differ significantly from that of normal horse serum globulins, the electrophoretic mobility does differ from those of normal serum components.

The molecular weight of diphtheria toxin is 70,000 and of antitoxin is 150,000.

From ultracentrifuge studies on the two reactants and on mixtures of toxin and antitoxin in soluble inhibition zones, the average molecular composition of the specific floccules at certain reference points throughout the equivalence zone and the maximum "valence" of toxin and antitoxin with respect to each other have been calculated.

The toxin-antitoxin complex is aggregated even in soluble regions of toxin and antitoxin excess. The equilibrium between aggregated and unaggregated forms is dependent on the concentration of the specific protein in excess.

The significance of the results was discussed in relation to antigen-antibody reactions in general.

Some Cellular Diffusion Processes Involving Hydrolytic Membrane Equilibria. M. H. JACOBS and A. K. PARPART (Department of Physiology, University of Pennsylvania, and Department of Biology, Princeton

University). Hydrolytic membrane equilibria are well illustrated by the behavior of the erythrocyte in the presence of various ammonium salts, singly and in different combinations. Three chief types of such salts may be distinguished: *a*, those of weak, so-called penetrating acids, which enter all cells with ease by a "molecular" type of penetration; *b*, those of strong mineral acids, to whose anions the erythrocyte is permeable, which enter it by a "molecular-ionic" mechanism consisting of the penetration of NH_3 followed by an exchange of OH' ions for other anions; and, *c*, those of acids to whose undissociated molecules and anions the erythrocyte is relatively impermeable.

In a mixture of two salts of types *a* and *c* the former in general tends to become unequally distributed between the cell and its surroundings in a manner that in some respects resembles and in others differs from the well-known Gibbs-Donnan ionic equilibrium. This unequal distribution explains the rapid but limited swelling that occurs on adding a salt of type *a* to erythrocytes suspended in solutions of ammonium citrate, but not of NaCl.

A mixture of salts of types *a* and *b* produces a similar swelling, which may be followed by exchanges of anions, thus permitting the process to proceed indefinitely. The rapid rate of entrance of NH_4Cl into erythrocytes by this mechanism in the presence of low concentrations of bicarbonates, sulphides and cyanides may in a certain sense be considered to be a catalyzed diffusion process.

The addition to a suspension of erythrocytes in ammonium citrate at pH 7 of a little saturated NaCl, by furnishing ions for which OH' can be exchanged, may cause marked swelling of the cells in spite of the increase in the external osmotic pressure. In the analysis of processes involving the penetration of ammonium salts, use may advantageously be made of the retardation of ionic exchanges, but not of certain types of molecular penetration, by butyl alcohol and related substances.

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